Clinical aspects and pathophysiological mechanisms of (systemic) right ventricular failure

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Chapter 1

General introduction and outline of this thesis

Clinical aspects and pathophysiological mechanisms of (systemic) right ventricular failure

General aspects of the left ventricle and right ventricle

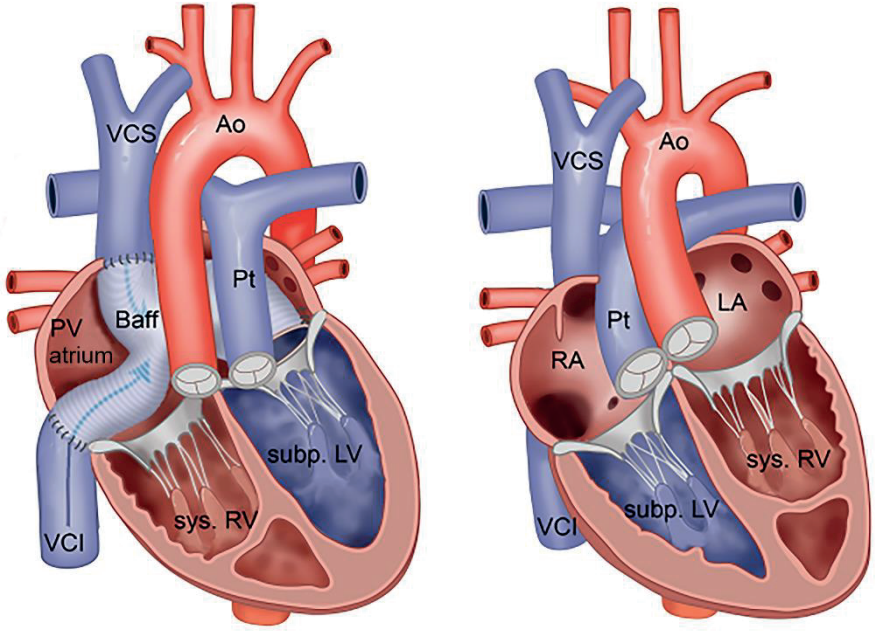
Proper cardiac performance to sustain the body depends heavily on an a well developed biventricular (left and right) anatomy and adequate function. In the normal heart, the right ventricle (RV) provides blood flow to the lungs and the left ventricle (LV) provides (oxygenated) blood flow to the systemic circulation. The LV and the RV are morphologically, developmentally, and functionally different (1). Generally, the RV has a smaller contractile reserve and, for its output, depends more on heart rate than the LV (2). In the past, scientific studies in the field of cardiac disease have initially focused more on the LV than on the RV. However, it has become increasingly clear that knowledge regarding the RV is also of great importance in many settings, such as in the setting of congenital heart disease, where in many patients the RV is the ventricle that is primarily affected. It has been recognized however, that findings derived from studies in the LV, can not be randomly extrapolated to the RV. For example, in cases of heart failure, the RV does not respond the same way to medication as the LV does (3) and information derived from randomized clinical trials based on large patients cohorts, are lacking in many instances. In addition, it is increasingly recognized that RV function may also contribute to prognosis in left sided heart disease. For example, independently of LV function, RV function may be the most important predictor of mortality in patients with ischemic or dilated cardiomyopathy and a reduced LV function (4).

Historical perspective of the systemic right ventricle

In specific cases, the focus on the RV is even more important. In the current thesis, the focus lies on patients with a RV in the systemic position in a biventricular circulation. Patients with a systemic RV comprise two main groups groups. The first group has been diagnosed with transposition of the great arteries (TGA) and received a physiological surgical correction with an atrial switch operation according to Mustard (5) or Senning (6). The second group of patients has been diagnosed with congenitally corrected TGA (ccTGA) (*Figure 1*).

After the era of Mustard and Senning, due to improved surgical techniques, the arterial switch operation became feasible, providing patients diagnosed with TGA with an anatomical correction, resulting in a systemic LV. During this procedure the great arteries are "switched", making the native aortic root, a neo-pulmonary trunk, whereas the pulmonary root becomes the neo-aorta, with re-implanted coronary arteries (7). For the ccTGA group, nowadays a "double switch operation" (i.e. performing both an atrial as well as arterial switch) is an option in selected patients, which also leads to the

restoration of the LV as the systemic ventricle. Despite these new treatment options, there are still several generations of patients with a systemic RV, currently mostly in their 30s, 40s, and 50s. Every new decade that this group faces, brings new clinical challenges which were unseen before. To be able to provide this group of patients with optimal health care, continuous monitoring and research efforts are necessary. This also encompasses the exploration of new management techniques that have proven efficient in patients with LV failure, but that have often not been evaluated yet in the smaller group of patients with (systemic) RV failure.



*(**Figure 1**): **TGA after atrial switch correction and ccTGA***
Ao: aorta; Baff: systemic venous baffle; LA: (morphologically) left atrium; Pt: pulmonary trunk; PV tunnel: pulmonary venous atrium; RA: (morphologically) right atrium; Subp. LV: subpulmonary LV; Sys. RV: systemic RV; VCI: inferior vena cava; VCS: superior vena cava

Development and epidemiology of TGA and ccTGA

TGA, representing about 5-8% of all adult congenital heart disease (8), is characterized by a concordant atrioventricular connection (i.e. the morphological right atrium drains to the morphological right ventricle, and the morphological left atrium drains to the morphological left ventricle) and a discordant ventriculo-arterial connection (i.e. the morphological right ventricle drains to the aorta and the morphological left ventricle drains to the pulmonary trunk). In complex forms, a hemodynamically relevant

ventricular septal defect and/or left ventricular outflow tract obstruction are also present. The course of great arteries and their outflow tracts is usually parallel in TGA, often with a right anterior position of the aortic orifice, which is a distinctive feature on for example echocardiography. During normal embryonic development, the entire outflow tract (later to be separated into left and right) is initially positioned above the RV. Due to asymmetric contributions of cells from the second heart field (the splanchnic mesoderm posterior to the heart, that contributes a.o. myocardium to the heart during development), the right ventricular outflow tract grows and thereby "pushes" the pulmonary trunk to its normal left anterior position, as related to the aorta (9-12). Variations/errors in this process of the so-called "pulmonary push" and anomalous development of the subpulmonary myocardium are thought to give rise to congenital heart defects with abnormal position of the great arteries, such as TGA, double outlet right ventricle, or tetralogy of Fallot (10, 12).

CCTGA is rarer than TGA, representing only about 1% of all adult congenital heart defects (13). It is characterized by both a discordant atrioventricular connection as well as a discordant ventriculo-arterial connection. As such, in uncomplicated cases, although the systemic ventricle is a RV, a functioning circulation is present at birth and problems may not arise until decades later (14). However, ventricular septal defects and left ventricular outflow tract stenosis are often present, and the tricuspid valve is regularly found to be structurally abnormal and may have Ebstein-like characteristics, making it prone to dysfunction. These associated anomalies can negatively influence the disease course of ccTGA (15). Less is known about the embryology of ccTGA. The heart defect is thought to (partly) arise through faulty looping of the primitive heart tube.

Autonomic function and cardiac disease

Function and dysfunction of the autonomic nervous system play an important role in cardiac disease and many treatments rely on its modification. The sympathetic system optimizes heart function for active or stress situations (fight or flight) and is responsible for increases in heart rate, conduction speed, and contractility. The parasympathetic system optimizes heart function for restorative states (rest and digest) by lowering these parameters, thus conserving energy. Generally, decreased cardiac autonomic function is associated with adverse prognosis in both primary and secondary prevention settings (16).

Cardiac autonomic innervation is involved in the pathophysiology of heart failure and arrhythmias, both of which are important problems in patients with a systemic RV.

Regarding heart failure, as a response to reduced cardiac output, the sympathetic branch of the autonomic nervous system becomes activated. Initially, sympathetic activation leads to restoration of cardiac output through increased inotropy on the cardiac level. On the long term, chronically increased catecholamine levels lead to downregulation of cardiac β-adrenergic receptors as a protective mechanism against myocardial norepinephrine toxicity, but this desensitization also leads to loss of adrenergic functional reserve (17, 18).

Compared to sympathetic involvement in heart failure, less is known about parasympathetic involvement. It is generally thought that, in contrast to sympathetic activity, parasympathetic activity in heart failure is cardioprotective, but that this is downregulated through pathophysiological mechanisms. Clinically, reduced parasympathetic tone can be observed for example as reduced baroreflex sensitivity, impaired heart rate deceleration after exercise, or reduced heart rate variability (HRV) in patients with heart failure (19-22). Briefly, HRV analysis quantifies the spontaneous fluctuations in heart rate. These are mainly caused by parasympathetic modulation, so generally, higher indices of HRV indicate higher parasympathetic activity which implies intact parasympathetic innervation, at least of the sinus node (23). Furthermore, heart rate turbulence (HRT) also provides information about parasympathetic function: HRT describes the pattern of acceleration and deceleration of heart rate after a premature ventricular complex, and reflects baroreflex function (24).

Regarding arrhythmias, the left atrial area around the pulmonary veins contains many ganglionated plexuses which receive sympathetic as well as parasympathetic output (25). Atrial fibrillation can be triggered by stimulation of these areas, and can be successfully treated with ablation of these sites. Atrial fibrillation can be sympathetically or parasympathetically mediated (26, 27). Changes in autonomic tone appear to immediately precede ventricular arrhythmias, as becomes clear through HRV analysis of ICD or Holter records (28-34). However, the direction of the changes and the exact parameters concerned are inconsistent and probably highly dependent on patient factors and specific etiology of the arrhythmia. Only an increase in heart rate preceding arrhythmias is consistently seen in these recordings (28-34).

Specifically in congenital heart disease, abnormal autonomic function is common and may result from abnormal development of innervation, altered hemodynamics, or thoracic surgery (35-37, 38). Abnormal autonomic function as a consequence of altered hemodynamics can for example be seen in patients with an atrial septal defect, where stretch of the sinoatrial node alters HRV (39). Another example is in coarctation of the aorta: here, renal hypoperfusion may lead to neurohumoral activation and

subsequently increased sympathetic output, despite adequate left ventricular function (40). Heart failure can also cause reduced autonomic function: for example, in adults with tetralogy of Fallot, reduced heart rate turbulence is correlated with reduced LVEF and RVEF (41). Cardiac nerves can be damaged and hemodynamics can be stressed during surgery, which may lead to a decrease in HRV immediately after surgery and an increase at longer follow-up, indicating nerve recovery and improved hemodynamic status (38). Generally, knowledge regarding asymmetry and heterogeneity in cardiac autonomic innervation, which is especially relevant in patients with a systemic RV, is scattered. In this thesis, **chapter 2** aims to link and summarize existing literature. Furthermore, in patients with a systemic RV, cardiac autonomic function has not yet systematically been quantified and correlated with clinical features and outcomes, such as arrhythmias, in adult patients. In this thesis, **chapters 3 and 4** address these gaps in current knowledge.

The systemic right ventricle in adult patients: (patho)physiology and complications

In the past decades, survival of patients with a systemic right ventricle has shown a vast improvement thanks to improved surgical and percutaneous techniques, expertise, routine follow-up, and focus on early detection of complications (42-44). This has confronted clinicians with problems previously unencountered as patients with complex cardiac anatomy and physiology reached the adult age and became older. Challenges have been posed by progressive heart failure, baffle leakage/stenosis, valvular defects, arrhythmias, and conduction disorders. These problems and their urgency in this group of relatively young patients with serious risks of morbidity and mortality have been increasingly recognized by the research agenda (44, 45).

Systemic right ventricular failure and tricuspid valve (systemic atrioventricular valve) regurgitation may arise in the course of the years due to progressive dilatation caused by the high systemic pressure to which the RV is exposed. Especially in ccTGA, this can be exacerbated by Ebstein-like structural valve defects. Endocarditis may cause additional valve damage. In patients post Mustard or Senning procedures, the atrial kick contributing to ventricular filling is virtually absent, due to the usually stiff baffle between the pulmonary veins and the systemic RV. Surgery may be considered in patients with progressive tricuspid valve regurgitation. Due to a high relapse rate of valve regurgitation after valvuloplasty, valve replacement is the preferred option (46).

Baffle-related complications may occur in patients after the atrial switch operation (Mustard/Senning). Obstruction of the systemic venous baffle may be chronic or acute. Chronic obstruction is usually accompanied by the formation of a collateral circulation and may therefore be asymptomatic (47). Balloon dilation with/without stenting or

surgical correction are possible treatments. Obstruction of the pulmonary venous conduit may be suspected in the case of turbulent high flows at the pulmonary veins as shown by Doppler echocardiography. Pulmonary venous obstruction may lead to pulmonary hypertension and should be surgically relieved (48). Baffle leakage can lead to shunting and puts the patient at risk for paradoxical emboli. The diagnosis can usually be made with transoesophageal echocardiography. The leakage may be treated interventionally or surgically (48).

Arrhythmias in patients with a systemic right ventricle, apart from bradycardias and other arrhythmias caused by conduction system damage/maldevelopment (see paragraph below), mostly consist of atrial flutter. Scarring at the atrial level can create areas prone to slow conduction, increased automaticity, and re-entry, predisposing to atrial flutter. These arrhythmias may be difficult to treat and further exacerbate systemic RV dysfunction (49). Specifically in ccTGA, arrhythmias may also be a consequence of congenital accessory pathways (49).

Conduction disorders in patients with a systemic right ventricle may also be due to scarring on the atrial level as a late complication of Mustard or Senning surgery. In patients with ccTGA, complete atrioventricular block is highly prevalent due to an anatomically abnormal and fragile conduction system, and may be caused by fibrosis of conduction fibres or a greater distance between the AV-node and the septum (50).

Generally, since major clinical events are common in patients with a systemic RV, a relatively simple risk score for the prediction of these events would be useful in follow-up and counselling. In this thesis, **chapter 6** incorporates data from multiple centers to address this question.

Routine follow-up, treatment, and imaging in patients with a systemic RV

In the 2020 ESC guidelines on congenital heart disease in adults, at least annual follow-up in a specialized adult congenital heart disease center is recommended, where special attention can be paid to the possible complications described above (48). For follow-up of the systemic RV function, echocardiography is described as the first-line diagnostic modality, which can provide information about a.o. the systemic RV size and function. Cardiac magnetic resonance imaging may provide more robust quantification of systemic RV function when compared with echocardiography. Echocardiography is more readily available and is also feasible in patients with devices and potentially present epicardial or abandoned leads, in contrast with cardiac magnetic resonance imaging (48, 51, 52). However, the complex three-dimensional shape of the systemic RV, its pronounced trabeculations, and the presence of a moderator band limits the

assessment of systemic RV function with echocardiography (53) which complicates routine assessment. Global longitudinal strain is a promising variable to quantify systemic RV function, as recent studies show (54). However, echocardiographic protocols for the routine follow-up of patients with a systemic RV have not been standardized, as it is currently unclear which echocardiographic variables correlate best with cardiac magnetic resonance imaging and are also feasible across the whole, heterogeneous group of patients with a systemic RV. In this thesis, this subject will be addressed in **chapter 5**.

Regarding medical treatment, no specific recommendations are currently made in the ESC guidelines. There is no strong evidence that heart failure medication improves outcome in patients with a systemic RV (48), although the angiotensin receptor blocker valsartan may slow the progression of systemic RV failure (55, 56), and the cautious use of ACE inhibitors and β-blockers may be beneficial in symptomatic patients (57). The European guidelines recommend considering diuretics for symptom relief and to prescribe heart rate-lowering drugs with caution because of the risk of brady-arrhythmias (48). For patients with heart failure with a normal biventricular circulation, sacubitril/valsartan has recently proven to improve outcome (58). For patients with a systemic RV, this drug has not yet been investigated. In this thesis, this subject will be addressed in **chapter 7**.

In adult patients with congenital heart disease, including patients with a systemic RV, it may be especially valuable to integrate home monitoring through eHealth in the follow-up routine: these patients are younger compared to the general population of cardiac patients, are likely to own a smartphone device, and have a high degree of digital literacy (59). In this thesis, the experience of titration of sacubitril/valsartan using eHealth smart technology in the cohort of **chapter 7** will be described in **chapter 8**.

For selected patients with a systemic RV and end-stage heart failure , ventricular assist device implantation in the failing systemic RV may be an option (60). In this thesis, **chapter 9** describes the first two cases in the Netherlands where this treatment was used.

Aim and outline

The aim of this thesis is to explore the systemic right ventricle from different interrelated angles. In part I, (patho)physiology and mechanisms, we have studied the anatomy and function of the autonomic nervous system in the setting of CHD with a systemic RV, as related to outcome. In part II, clinical applications, we aimed to predict and monitor clinical deterioration, and to explore treatment options of complications

accompanying the circulation with a systemic right ventricle. **Part I** of this thesis consists of **chapters 2-4**. In **chapter 2**, the differences between the LV and the RV regarding cardiac autonomic innervation are reviewed. In **chapters 3 and 4,** noninvasive measures of cardiac autonomic function are investigated in a group of patients with a systemic RV and related to clinical outcome. **Part II** of this thesis consists of **chapters 5-8**. In **chapter 5**, different imaging modalities are compared and from these data, the most reliable and practical echocardiographic measures of systemic RV function are extracted. In **chapter 6**, the patterns of the clinical course and a prediction model of clinical outcome in patients with a systemic RV are described. **Chapter 7** reports on the first results of the treatment of systemic RV failure with the drug sacubitril/valsartan. **Chapter 8** describes the experience of titration of sacubitril/valsartan using eHealth smart technology in the cohort of **Chapter 7**. Finally, **chapter 9** describes the first two cases of implantation of a ventricular assist device in patients with a systemic RV in the Netherlands.

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Part I: (patho)physiology and mechanisms

Chapter 2

Asymmetry and Heterogeneity: Part and Parcel in Cardiac Autonomic Innervation and Function

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Abstract

The cardiac autonomic nervous system (cANS) regulates cardiac adaptation to different demands. The heart is an asymmetrical organ, and in the selection of adequate treatment of cardiac diseases it may be relevant to take into account that the cANS also has sidedness as well as regional differences in anatomical, functional, and molecular characteristics. The left and right ventricles respond differently to adrenergic stimulation. Isoforms of nitric oxide synthase, which plays an important role in parasympathetic function, are also distributed asymmetrically across the heart. Treatment of cardiac disease heavily relies on affecting left-sided heart targets which are thought to apply to the right ventricle as well. Functional studies of the right ventricle have often been neglected. In addition, many principles have only been investigated in animals and not in humans. Anatomical and functional heterogeneity of the cANS in human tissue or subjects is highly valuable for understanding left- and right-sided cardiac pathology and for identifying novel treatment targets and modalities. Within this perspective, we aim to provide an overview and synthesis of anatomical and functional heterogeneity of the cANS in tissue or subjects, focusing on the human heart.

Introduction

The cardiac autonomic nervous system (cANS) adapts the responses of the heart to external demands. It consists of a sympathetic part, which adapts cardiac function to physical activity and stress, and a parasympathetic part, which adapts it to a resting and restorative state. Under physiological conditions these systems are balanced and cardiac responses will be fine-tuned to differentiating demands. Under pathophysiological conditions, dysregulation of the cANS can occur as a result of for example cardiac damage and/or failure, and consequently the balance between the sympathetic and parasympathetic activity is lost. Usually, this is caused by an increased activity of the sympathetic part of the cANS and/or diminished activity of the parasympathetic part and is associated with an adverse prognosis.

Knowledge about the cANS is necessary for understanding cardiac disease and for the identification of treatment targets (*Vegh et al., 2016*). Much knowledge is derived from studies in patients with left-sided pathology, such as myocardial infarction or left ventricular failure (*Cao et al., 2000; Fallavollita et al., 2014; Fukuda et al., 2015; Matsuo et al., 2016; Franciosi et al., 2017*). The same principles are considered to apply to the right ventricle (RV). However, the RV is developmentally, morphologically, and functionally different from the left ventricle (LV). Traditional heart failure medication used in

patients with left ventricular failure, relying heavily on influencing the cANS, may not have the same effect on patients with congenital heart disease and right ventricular failure, even though the hemodynamic problem is similar (*Hechter et al., 2001; Lester et al., 2001; Robinson et al., 2002; Dore et al., 2005; Josephson et al., 2006; Doughan et al., 2007; Giardini et al., 2007; Therrien et al., 2008; Bouallal et al., 2010; Tutarel et al., 2012; Dos et al., 2013; van der Bom et al., 2013; Palma and Benarroch, 2014; Tobler et al., 2017*). Likewise, other cardiac diseases show a relation to cardiac sidedness and region and are heavily influenced by autonomic innervation, such as cardiac arrhythmias originating from the region of the pulmonary veins, ligament of Marshall and the RV outflow tract (*Wickramasinghe and Patel, 2013*).

Although several reports describe the human heart and cANS, a detailed overview focusing specifically on anatomical sidedness and regional differences in cardiac autonomic innervation as related to function, is currently lacking. The selection of adequate treatment, the identification of future treatment targets, the planning of cardiothoracic surgery and catheter ablation procedures for arrhythmias, as well as the use of thoracic epidural anesthesia might be optimized by taking the sidedness and regional differences of the cANS into consideration.

The aim of the current paper is to review the anatomy and physiology of the human cANS with special emphasizes on asymmetry and regional differences in peripheral cardiac autonomic regulation. For a comprehensive overview of central regulation of cardiac autonomic function, we refer to previous excellent work (*Anderson et al., 2000; Kirby, 2007; Kawashima, 2011; Hasan, 2013; Palma and Benarroch, 2014; Jamali et al., 2016; Coote and Spyer, 2018*). Data from animal studies are cited when human data are unavailable or when data from animal studies offer additional insight. Relevant questions for future research are formulated.

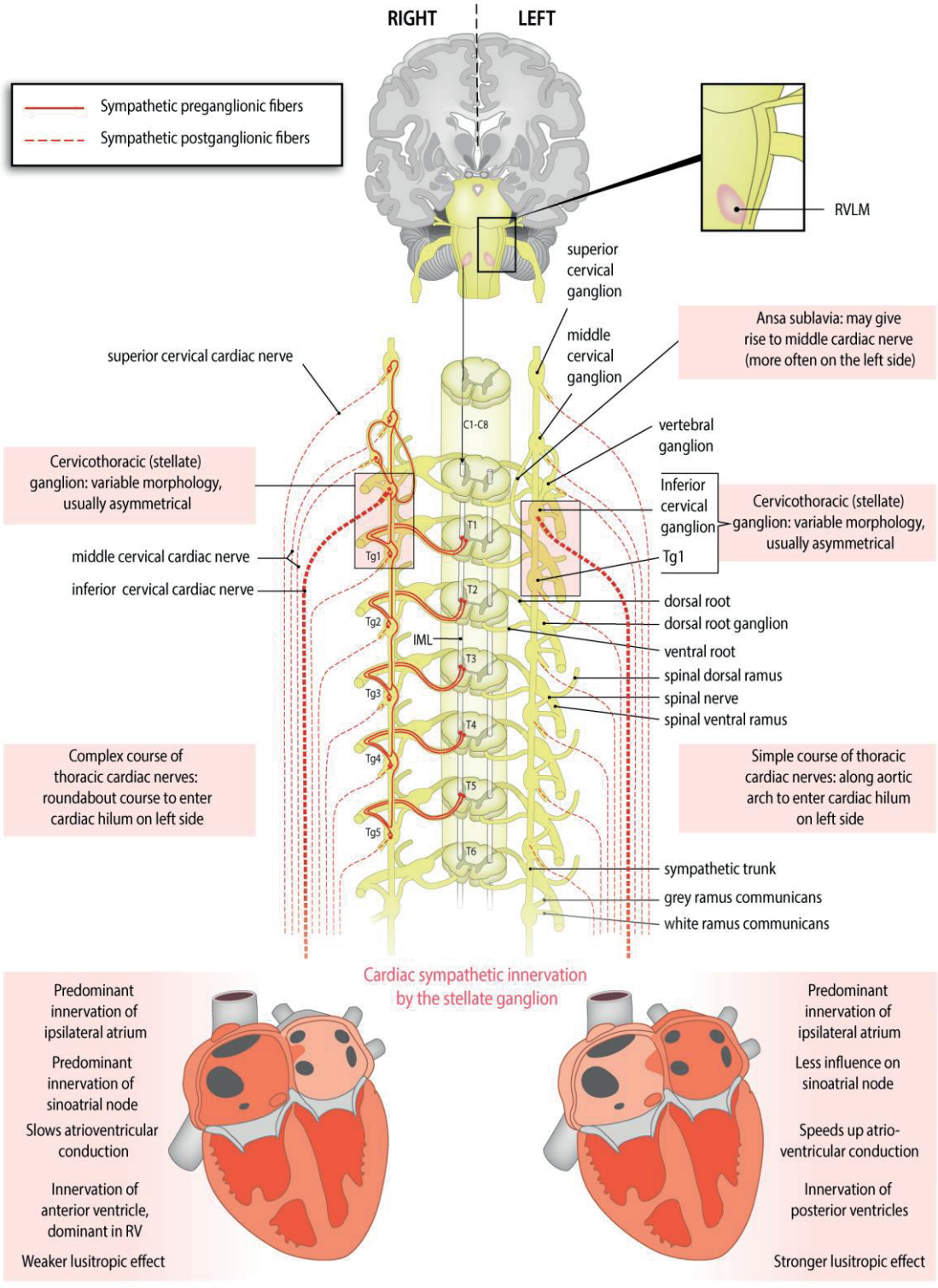
RIGHT
LEFT
Sympathetic preganglionic fibers
Sympathetic postganglionic fibers
RVLM
superior cervical ganglion
Ansa sublavia: may give rise to middle cardiac nerve (more often on the left side)
middle cervical ganglion
superior cervical cardiac nerve
vertebral ganglion
C1-C8
Cervicothoracic (stellate) ganglion: variable morphology, usually asymmetrical
Inferior cervical ganglion
Cervicothoracic (stellate) ganglion: variable morphology, usually asymmetrical
Tg1
middle cervical cardiac nerve
inferior cervical cardiac nerve
T1
T2
Tg2
IML
T3
Tg3
T4
Tg4
T5
Tg5
T6
dorsal root
dorsal root ganglion
ventral root
spinal dorsal ramus
spinal nerve
spinal ventral ramus
Complex course of thoracic cardiac nerves: roundabout course to enter cardiac hilum on left side
Simple course of thoracic cardiac nerves: along aortic arch to enter cardiac hilum on left side
sympathetic trunk
grey ramus communicans
white ramus communicans
Cardiac sympathetic innervation by the stellate ganglion
Predominant innervation of ipsilateral atrium
Predominant innervation of sinoatrial node
Slows atrioventricular conduction
Innervation of anterior ventricle, dominant in RV
Weaker lusitropic effect
Predominant innervation of ipsilateral atrium
Less influence on sinoatrial node
Speeds up atrio-ventricular conduction
Innervation of posterior ventricles
Stronger lusitropic effect

Figure 1: Anatomy of the sympathetic cardiac autonomic nervous system: asymmetry and regional differences.

Top part: sympathetic cardiac autonomic nervous system. Preganglionic cardiac sympathetic axons (red, solid lines) arise from neurons of the intermediolateral (IML) cell columns in the upper four or five thoracic segments of the spinal cord. These neurons receive excitatory input from the rostral ventrolateral medulla (RVLM). The preganglionic fibers leave the spinal cord through ventral (anterior) roots, enter the ventral (anterior) rami of spinal nerves and pass to the sympathetic chain through white rami communicantes to synapse in the upper thoracic ganglia (Tg) or cervical ganglia; postganglionic fibers (red, dotted lines) from these ganglia form the sympathetic cardiac nerves. At the heart parasympathetic and sympathetic nerves converge to form the cardiac plexus from which atrial and ventricular autonomic innervation is arranged. Sided and regional differences in anatomy are indicated in the boxes. Bottom part: functional anatomy of cardiac sympathetic innervation by the right and left stellate ganglia. Sided and regional differences in function are indicated in the boxes. The right stellate ganglion greatly increases heart rate, slows the atrioventricular conduction, influences the right atrium more strongly than the left, shortens the QT interval, contributes to some extent to myocardial relaxation, and is the predominant source of sympathetic innervation in the right ventricle and the anterior part of both ventricles. The left stellate ganglion increases heart rate to some extent, speeds up the atrioventricular conduction, influences the left atrium more strongly than the right, lengthens the QT interval, contributes greatly to myocardial relaxation, and is the predominant source of sympathetic innervation of the posterior part of the ventricles.

Sympathetic Ganglia and Nerves: Anatomical Evidence of Origins, Variations and Asymmetry (Figure 1)

Preganglionic cardiac sympathetic fibers originate from neurons located in the intermediolateral cell columns of the upper thoracic spinal cord (usually T1-T4 or T5) and exit the spinal cord through the ventral (anterior) roots of spinal nerves (*Figure 1, top part*). Subsequently, they synapse on postganglionic sympathetic neurons in the paravertebral ganglia of the sympathetic trunk. The sympathetic trunk is a bilateral structure situated left and right paravertebrally, extending from the cervical to the coccygeal level. The following ganglia of the sympathetic trunk may provide postganglionic fibers to the heart: the left and right superior cervical, middle cervical and vertebral ganglia, the left and right cervicothoracic ganglion (also called stellate ganglion, composed of the inferior cervical ganglion and the first thoracic ganglion), and the upper thoracic ganglia on both sides. However, there still is debate about the upper and lower limits from which postganglionic fibers to the heart originate, and significant interindividual variations exist (*Bonica, 1968; Janes et al., 1986; Kawashima, 2011) (reviewed in Wink et al., 2020*). Postganglionic sympathetic fibers travel as cardiac nerves from these ganglia toward the cardiac plexus. Defined by the paravertebral ganglion they originate from, these nerves are named as follows (*Figure 1A*): the superior cervical cardiac nerve (originating from the superior cervical ganglion or sympathetic trunk between the superior cervical and middle cervical ganglia), the middle cervical cardiac nerve (originating from the middle cervical ganglion or the

vertebral ganglion, or from the sympathetic trunk between the middle cervical and the inferior cervical or cervicothoracic/stellate ganglia, including the ansa subclavia), the inferior cervical cardiac nerve (originating from the inferior cervical ganglion or the cervicothoracic/stellate ganglion), or thoracic cardiac nerves (originating from the thoracic ganglia or the thoracic sympathetic trunk below the inferior cervical or cervicothoracic/stellate ganglion) (*Kawashima, 2005; Federative International Programme for Anatomical Terminology, 2019*)

Variations and asymmetry in stellate ganglion morphology and cardiac sympathetic nerve origin have been described. In an American human cadaver study, it was observed that the right stellate ganglion was often longer than the left (*Kwon et al., 2018*). However, in a cohort from Switzerland, the left stellate ganglion was longer (*Marcer et al., 2012*) and in a Chinese cohort, no differences in length were found between the left and right stellate ganglion (*Yin et al., 2015*). A study of Pather in humans in South Africa, also reported no significant difference in the length and width of the right and left sides of the adult cardiothoracic ganglia (*Pather et al., 2006*). In these studies, differing occurrence and asymmetry of the left and right stellate ganglion as well as the other thoracic sympathetic ganglia is consistently described.

A middle cardiac cervical nerve originating from the ansa subclavia (nerve connection between the middle and inferior cervical ganglia) was observed twice as often on the left compared to the right (*Kawashima, 2005*). Furthermore, asymmetry in the origin and courses of the left and right thoracic cardiac nerves originating from the lower thoracic ganglia (fourth or fifth) was observed (*Fukuyama, 1982; Kawashima, 2005*). The left lower thoracic cardiac nerves follow a simple course along the aortic arch and thoracic aorta, comparable with most other cardiac nerves, which generally run along the great arteries. In contrast, the right lower thoracic cardiac nerves may descend obliquely along the intercostal vessels, turn and ascend along the thoracic aorta, to finally reach the heart through the right venous part of the cardiac hilum or by connecting to the cardiac plexus. This complex, 'roundabout' course may be related to remodeling/regression of the right aortic arch during embryonic development, whereas the left sided arch persists (*Gittenberger-de Groot et al., 2006; Kawashima, 2011*).

Cardiac Areas of Sympathetic Innervation by the Left and Right Stellate Ganglion: Functional Evidence (Figure 1 and Table 1)

The stellate ganglia play important and differing roles in cardiac autonomic function and have been studied extensively. The right stellate ganglion is primarily responsible for increasing the heart rate and slowing atrioventricular conduction, whereas the left stellate ganglion has little effect on heart rate and increases atrioventricular conduction (*Figure 1, bottom part*). This was concluded from functional studies in humans. A right stellate ganglion block leads to a marked decrease in heart rate, whereas left stellate ganglion block leads to a more discrete decrease in heart rate (*Rogers et al., 1978; Yokota et al., 2013*). Furthermore, it was demonstrated that right stellate ganglion block leads to faster atrioventricular conduction and left stellate ganglion block leads to slower atrioventricular conduction (*Cinca et al., 1985*). Interestingly, a dog study suggested that the left stellate ganglion dominates over the right in terms of ventricular refractoriness: left stellate ganglion block led to a net increase in refractoriness, suggesting a decreased sensitivity to ventricular arrhythmias. However, while right stellate ganglion block produced a similar effect in absence of a functional left stellate ganglion, right stellate ganglion block led to a net decrease in refractoriness in the presence of a functional left stellate ganglion. This suggests an overshoot in compensatory sympathetic activity from the left stellate ganglion (*Schwartz et al., 1977*). Similarly, in humans, left stellate ganglion block shortens the corrected QT interval, whereas right stellate ganglion block lengthens it, suggesting a potential factor in arrhythmogenesis (*Egawa et al., 2001*). In line with this, left stellate ganglion block is increasingly used to treat ventricular arrhythmias (*Meng et al., 2017*). Other studies elaborate further on this topic (*Lane and Schwartz, 1987; Schwartz et al., 1992; Zhou et al., 2008*).

A block of either stellate ganglion in humans, led to prolonged atrial refractory time and a reduction in inducibility of atrial fibrillation. Each stellate ganglion may predominantly innervate the ipsilateral atrium, which, in turn, relays signals to the contralateral atrium (*Leftheriotis et al., 2016*).

The right stellate ganglion and left stellate ganglion influence both ventricles but unevenly. These regional differences were firstly demonstrated in dogs: the right stellate ganglion primarily influenced the anterior part of the LV and RV, whereas the left stellate ganglion primarily influenced the posterior LV and RV (*Yanowitz et al., 1966*). Similar to human studies, in this study QT-prolongation was observed after ablation of the right stellate ganglion and after stimulation of the left stellate ganglion (*Yanowitz et al., 1966*). A similar pattern was found in pigs: stimulation of the right

stellate ganglion led to increased echocardiographic radial and circumferential strain in the anterior regions, whereas stimulation of the left stellate ganglion led to increased strain in the inferior/posterior regions (*Zhou et al., 2013*). This pattern was confirmed by measuring activation-recovery intervals in another pig study (*Vaseghi et al., 2013*). Additionally, a study by Schlack and Thamer (*Schlack and Thamer, 1996*) in dogs demonstrated an improved lusitropic (myocardial relaxation) effect by left stellate ganglion stimulation compared with an impaired relaxation upon right stellate ganglion stimulation. These authors also demonstrated a higher global contractility increase with left stellate ganglion stimulation compared with right stellate ganglion stimulation. In the RV, innervation of the right stellate ganglion may predominate: in a study in dogs, right stellate ganglion stimulation shortened the refractory period more strongly in the RV than in the LV. Left stellate ganglion stimulation shortened the refractory period of the LV and the RV equally (*Garcia-Calvo et al., 1992*). Whether the same patterns in the ventricles are present in humans, and whether the distribution of innervation is influenced by the dominance of the coronary system, is unknown. It is considered that these differences in effects from the left and right stellate ganglia may play a role in arrhythmias, especially when their activity is unbalanced (*Lane and Schwartz, 1987*).

Parasympathetic Innervation: Anatomical Evidence of Origins and Contributions From Left and Right Vagal Cardiac Branches (Figure 2)

Preganglionic cardiac parasympathetic fibers originate from neurons located in the nucleus ambiguus and the dorsal motor nucleus of the vagus nerve and reach the heart through cardiac branches of this nerve (*Standring and Gray, 2016*). The vagus nerves (tenth cranial nerve) originate bilaterally from the medulla oblongata and give rise to a recurrent laryngeal nerve that differs in origin (branching site) and course on the two sides. Parasympathetic cardiac branches from these nerves are defined according to their origin as follows (*Figure 2, top part*): the superior cervical cardiac branch originates from the vagus nerve proximal to the branching site of the recurrent laryngeal nerve. A branch originating from any part of the recurrent laryngeal nerve is called an inferior cervical cardiac branch, and the cardiac branch originating from the vagus nerve distal to the branching site of the recurrent laryngeal nerve is called a thoracic cardiac branch (*Kawashima, 2005; Federative International Programme for Anatomical Terminology, 2019*).

Table 1: Summary of functional characteristics of the right and left sided ganglion stellatum*

Right stellate ganglion	**Left stellate ganglion**
Predominant innervation ipsilateral atrium ++	Predominant innervation ipsilateral atrium ++
Innervation contralateral atrium +	Innervation contralateral atrium +
Predominant innervation of anterior part both ventricles (dogs)	Predominant innervation of posterior part both ventricles (dogs)
Echocardiographic radial and circumferential strain in the anterior regions of the LV ↑ (pigs)	Echocardiographic radial and circumferential strain in the inferior/posterior regions of the LV ↑ (pigs)
Predominant innervation of RV (dogs)	
Myocardial relaxation (lusitropy) + (dogs)	Myocardial relaxation (lusitropy) ++ (dogs)
Myocardial contractility +	Myocardial contractility ++
Cardiac conduction system	
Heart rate ↑↑	Heart rate ↑/=
AV conduction ↓	AV conduction ↑
QT interval ↓	QT interval ↑
Right stellate ganglion block	**Left stellate ganglion block**
Heart rate ↓↓	Heart rate ↓
AV conduction ↑	AV conduction ↓
QTc interval ↑	QTc interval ↓
Atrial refractory time ↑	Atrial refractory time ↑
AF inducibility ↓	AF inducibility ↓

** data derived from human studies, unless otherwise indicated-for references see text*

While all cardiac branches are consistently seen on the right side, on the left side, the thoracic cardiac branch was absent in 45% of cases (*Kawashima, 2005*). In contrast to the preganglionic cardiac sympathetic fibers, which synapse on postganglionic neurons within ganglia of the sympathetic trunk (i.e., remote from the heart), preganglionic cardiac parasympathetic fibers synapse on postganglionic neurons within ganglionated plexuses embedded in the epicardial fat pads and the heart wall. To our knowledge, no further information is available about variations and asymmetry in the parasympathetic cardiac branches.

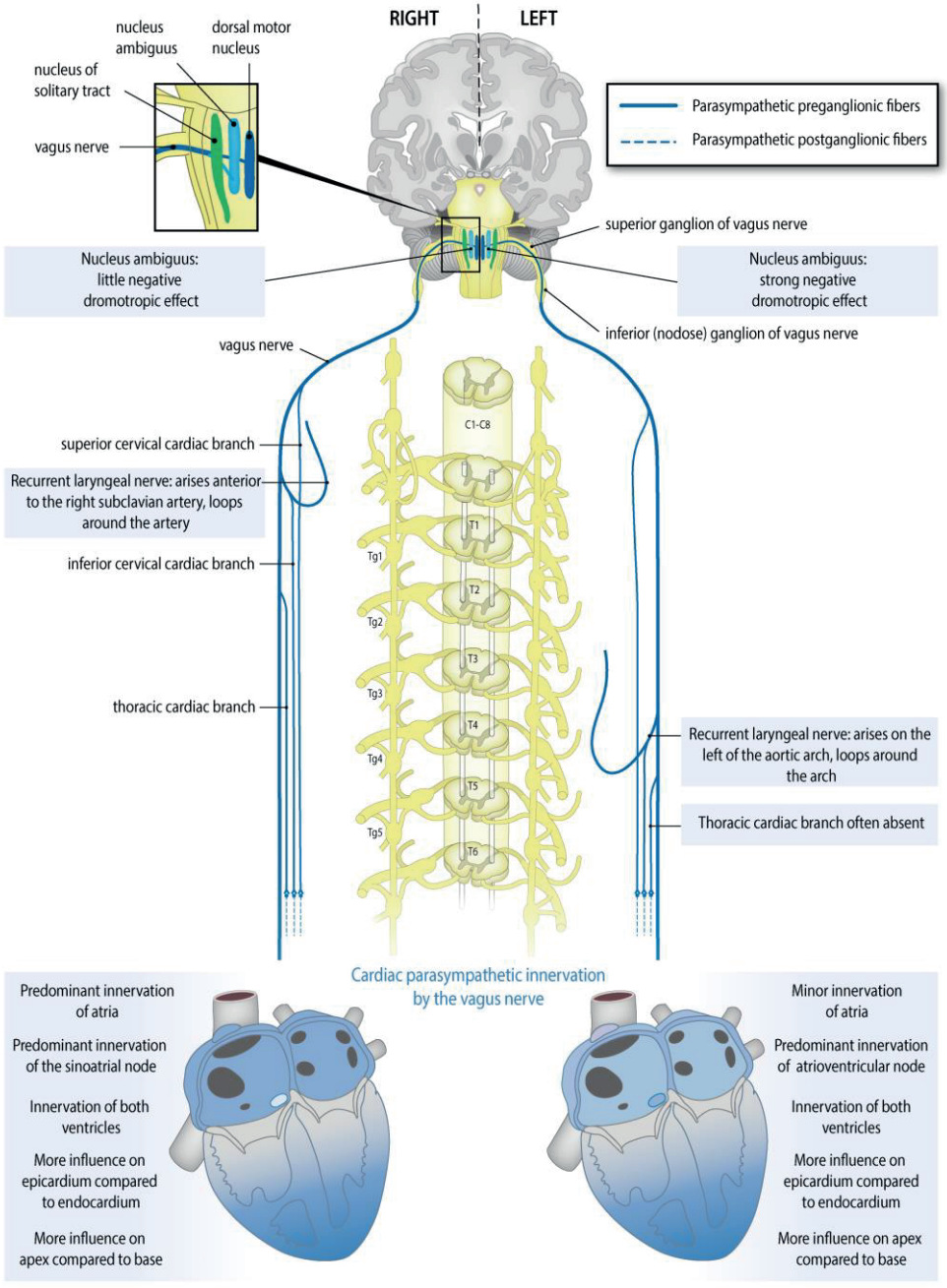
RIGHT
LEFT
nucleus ambiguus
dorsal motor nucleus
nucleus of solitary tract
vagus nerve
Parasympathetic preganglionic fibers
Parasympathetic postganglionic fibers
superior ganglion of vagus nerve
Nucleus ambiguus: little negative dromotropic effect
Nucleus ambiguus: strong negative dromotropic effect
inferior (nodose) ganglion of vagus nerve
vagus nerve
C1-C8
superior cervical cardiac branch
Recurrent laryngeal nerve: arises anterior to the right subclavian artery, loops around the artery
T1
Tg1
inferior cervical cardiac branch
T2
Tg2
T3
Tg3
thoracic cardiac branch
T4
Tg4
Recurrent laryngeal nerve: arises on the left of the aortic arch, loops around the arch
T5
Tg5
Thoracic cardiac branch often absent
T6
Cardiac parasympathetic innervation by the vagus nerve
Predominant innervation of atria
Predominant innervation of the sinoatrial node
Innervation of both ventricles
More influence on epicardium compared to endocardium
More influence on apex compared to base
Minor innervation of atria
Predominant innervation of atrioventricular node
Innervation of both ventricles
More influence on epicardium compared to endocardium
More influence on apex compared to base

Figure 2: Anatomy of the parasympathetic cardiac autonomic nervous system: asymmetry and regional differences.
Top part: parasympathetic cardiac autonomic nervous system. Preganglionic cardiac parasympathetic axons (blue, solid lines) arise from neurons in either the nucleus ambiguus or dorsal vagal nucleus; they run in cardiac branches of the vagus nerve to synapse in cardiac plexuses and ganglia from where postganglionic fibers (blue, dotted lines) innervate the sinoatrial node (SAN), atrioventricular node (AVN), coronary arteries, and ventricular myocytes. Sided and regional differences in anatomy are indicated in the boxes. Bottom part: functional anatomy of the right and left vagal nerves. Sided and regional differences in function are indicated in the boxes. The right vagus nerve greatly slows heart rate, may influence the atria more than the left vagus nerve, slows atrioventricular conduction to some extent, influences the epicardium more strongly than the endocardium and influences the apex more strongly than the base. The left vagus nerve slows heart rate to some extent, may influence the atria less than the right vagus nerve, greatly slows atrioventricular conduction, influences the epicardium more strongly than the endocardium and influences the apex more strongly than the base.

Cardiac Areas of Parasympathetic Innervation by the Left and Right Vagus Nerve: Functional Evidence (Figure 2 and Table 2)

The human sinoatrial node and atria are most likely predominantly influenced by the right vagus nerve, the atrioventricular node is predominantly influenced by the left vagus nerve, and the ventricles are influenced at least by the left vagus nerve but likely by both vagus nerves (*Banzett et al., 1999; Lewis et al., 2001; Muppidi et al., 2011; Figure 2, bottom part*). Although human studies are scarce, animal studies are in accordance with this: in the isolated rabbit heart, stimulation of the right vagus nerve had a stronger effect on heart rate, whereas the left vagus nerve had a stronger effect on atrioventricular conduction (*Ng et al., 2001*). This group also used the same model to explore this in the context of so-called accentuated antagonism (generally, vagal stimulation has a stronger effect when a background level of sympathetic activity is present). During sympathetic stimulation, right and left vagal nerve stimulation may reduce the heart rate differently: there was a trend toward a stronger effect of the right vagus nerve, although this result was not statistically significant (*Brack et al., 2004*). Animal research also reveals possible regional differences: in pigs, left or right vagus nerve stimulation had a stronger effect on the endocardium than on the epicardium and also on the apex compared to the base. This study also demonstrates that in pigs at least the LV is influenced by both vagus nerves (*Yamakawa et al., 2014*).

Table 2: Summary of functional characteristics of the right and left sided vagus nerves*

Right vagus nerve	Left vagus nerve
Innervation atria ++?	Innervation atria +?
Sino-atrial node	AV node
Both ventricles	Both ventricles
Influence on endocardium > influence epicardium (pig)	Influence on endocardium > influence epicardium (pig)
Influence on apex > influence on base (pig)	Influence on apex > influence on base (pig)
Cardiac conduction system	
Heart rate ↓↓ (rabbit)	Heart rate ↓
AV conduction ↓	AV conduction ↓↓

**Data derived from human studies, unless otherwise indicated-for references see text.*

Cardiac Afferent Nerve Fibers: Asymmetry and Regional Differences, Anatomical and Functional Aspects

Although visceral afferent fibers, in a strict sense, are not part of the autonomic nervous system (*Armour, 1999*), given their clinical relevance, regional and asymmetrical features of the afferent (sensory) part of the cardiac nervous system are also considered here. Cardiac afferent nerve fibers are an integral part of the regulatory pathways the cANS is involved in, and transfer sensory signals from the heart to the central nervous system, where they may activate efferent neurons through feedback loops. They convey cardiac nociceptive and reflexive information (*Armour, 1999; Kirby, 2007*). Like cardiac efferent (autonomic) nerves, these afferents demonstrate regional differences and asymmetry. Studies conducted in humans are rare and most knowledge regarding the organization and function of the cardiac afferent system is derived and extrapolated from animal studies.

The neurites (dendrites) of cardiac afferent neurons are located in the myocardium and their cell bodies lie in the dorsal root ganglia of spinal nerves or the inferior ganglion of the vagus nerve (nodose ganglion) (*Anderson et al., 2000; Kirby, 2007; Palma and Benarroch, 2014*).

Cardiac spinal or "sympathetic" afferents (named as such because their fibers accompany sympathetic efferent (autonomic) fibers retrogradely in splanchnic nerves) convey mainly nociceptive sensory information from the heart via the splanchnic nerves, sympathetic trunk, spinal nerve and dorsal root (dorsal root ganglia) to the

posterior horn of the spinal grey matter, where they synapse on second-order neurons of lamina I. The nociceptive information is further conveyed via ascending pain pathways to the thalamus and other brain regions involved in cardiac pain perception (*Palma and Benarroch, 2014*). When spinal cardiac afferents are involved in feedback loops via local interneurons projecting to the intermediolateral cell columns of the spinal cord, they can influence sympathetic efferent (motor) activity directly (*Armour, 1999; Anderson et al., 2000; Kirby, 2007; Palma and Benarroch, 2014*).

Some sympathetic afferents (mainly C-fibers, which are unmyelinated and are slow-conducting) produce substance P as their neurotransmitter. Substance P mediates nociception and also has efferent effects. Nerves containing substance P in the human heart are especially found around coronary arteries and other small blood vessels, and inside intrinsic cardiac ganglia (*Weihe et al., 1981; Rechardt et al., 1986; Laine et al., 2000; Hoover et al., 2009*). Substance P may be upregulated under pathological conditions. In conditions of ischemia-reperfusion, substance P can have a beneficial effect through increasing coronary blood flow (which was demonstrated in dogs). Conversely, in non-ischemic conditions such as myocarditis and volume overload, substance P may contribute to inflammation, apoptosis, and long-term reduction of LV-function (as was shown in various rodent models) (*Dehlin and Levick, 2014*).

Cardiac vagal afferents, of which unmyelinated, slow-conducting C-fibers constitute an important part, as was shown in studies in amongst others dogs and rats (*Ditting et al., 2005*) run centrally in the vagus nerves and convey mainly reflexive (mechano- and chemosensory) information from the heart via the nodose ganglion to the (caudal part of the) solitary nucleus (nucleus tractus solitarii) (*Figure 2, top part*). They can activate feedback loops through the thalamus and the parabrachial nucleus, and nucleus ambiguus, which lead to increased parasympathetic or decreased sympathetic outflow to the heart (*Armour, 1999; Kirby, 2007; Palma and Benarroch, 2014*). Of interest, cardiac afferent fibers have also been described to interact directly with postganglionic sympathetic neurons in the stellate ganglia and with parasympathetic postganglionic neurons or interneurons in the intrinsic cardiac ganglia, forming part of intrathoracic feedback loops, bypassing the central nervous system (*Crick et al., 2000; Kirby, 2007*).

The distribution of cardiac afferent nerve fibers in human can differ per cardiac region. The often observed bradycardia specifically accompanying inferoposterior myocardial infarctions may be a consequence of activation of vagal afferents on the inferior wall of the LV which trigger parasympathetic reflexes (*Perez-Gomez et al., 1979; Flapan et al., 1993*). The same pattern was observed in an experimental study in dogs (*Thames et al., 1978*). Interestingly, patients with an anterior myocardial infarction also had worse

baroreflex sensitivity and heart rate variability at follow-up compared with patients with inferior/posterior infarctions, which may also be due to this distribution, although it must be noted that the left ventricular ejection fraction was also lower in the anterior infarction group (*La Rovere et al., 1998*).

Distribution of vagal afferents in the heart was studied in guinea pigs by retrograde labeling of the nodose ganglia. Most vagal afferents were concentrated in the posterior atrial wall (mostly on the ipsilateral atrium of the labeled nodose ganglion), the pulmonary arterial wall, and around the coronary arteries (*Quigg et al., 1988*). From a physiological study in cats, it was concluded that cardiac afferents (vagal or spinal not specified) were located throughout the heart wall. In the ventricles, they were present mostly in the endocardium. In the atria, they were present equally endo- and epicardially (*Malliani et al., 1973*).

In conclusion, the anatomy and physiology of cardiac afferents are still largely to be elucidated, especially in humans.

Asymmetry of the Cardiac Plexus and Coronary Cardiac Nerves: Anatomical Evidence (Figure 3)

Human left and right sympathetic and parasympathetic cardiopulmonary nerves connect in the mediastinum, where they form the cardiac plexus. A distinction is made between the superficial (ventral) cardiac plexus, located in between the pulmonary trunk and aortic arch, and the deep (dorsal) cardiac plexus, located between the aorta and trachea (*De Gama et al., 2012; Figure 3*). The superficial and deep cardiac plexuses are not as discrete and confined as for example the cervical and thoracic paravertebral ganglia, but rather describe the locations of interconnecting nerve networks where the number of nerve fibers gradually increases and nerve fibers tend to be more mixed (including sympathetic, parasympathetic and visceral afferent fibers). Plexus formation tends to start higher on the right side (level of the brachiocephalic trunk) than on the left side (level of the aortic arch) (*Kawashima, 2011; Figure 3; Table 3*). Possibly, this can be attributed to regional differences during embryonic development, as the initially symmetrical pharyngeal arch arterial system, giving rise to part of the putative arterial vasculature, will show a left-sided dominance, with disappearance of the right sixth pharyngeal arch artery and disappearance/remodeling of the right aortic arch artery. The right fourth pharyngeal arch artery will form the proximal part of the right subclavian artery, below which the right laryngeal recurrent nerve will eventually course (*Gittenberger-de Groot et al., 2006*).

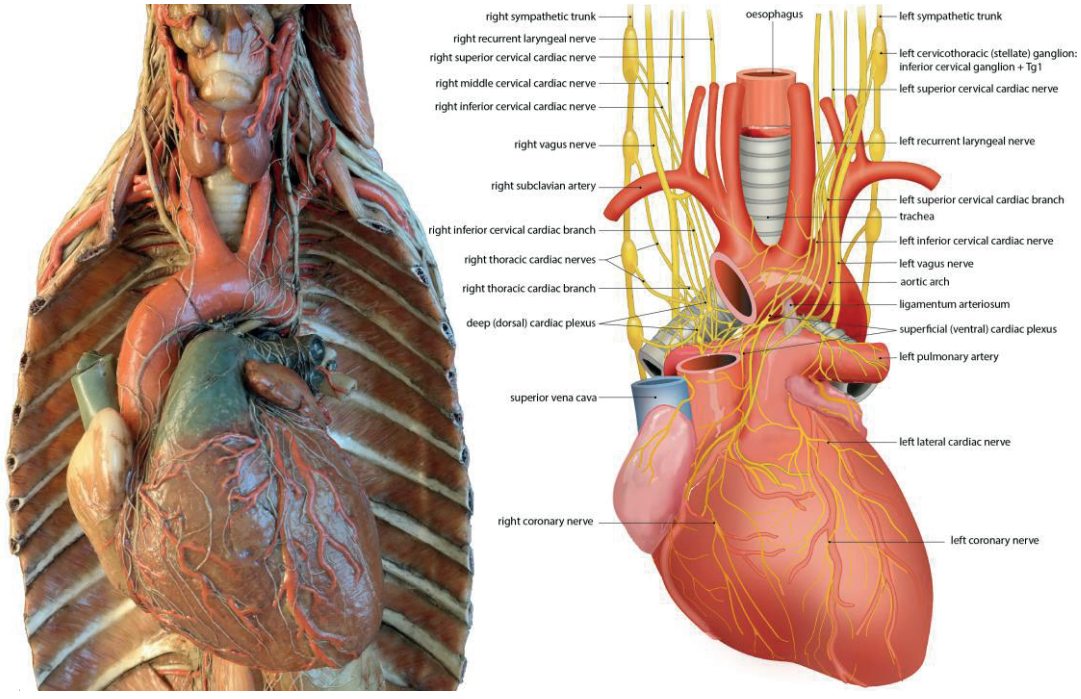

Figure 3: The left and right cardiac nerves and superficial and deep cardiac plexus.
Left: wax mold (Museo delle Cere Anatomiche "Luigi Cattaneo", Bologna, Italy) demonstrating sympathetic and parasympathetic (vagal) cardiac nerves and superficial and deep cardiac plexus. Photomicrograph courtesy of Dr. E.A.J.F. Lakke. With permission of the Museo delle Cere Anatomiche "Luigi Cattaneo", University Museum System, Alma Mater Studiorum – University of Bologna, Italy. Right: annotated drawing, details depiction of cardiac nerves and plexus depicted in the left panel. At the heart sympathetic and parasympathetic nerves converge to form the superficial and deep cardiac plexus from which atrial and ventricular autonomic innervation is arranged. For further explanation see text.

Among many smaller nerves, three large mixed nerves arise from these plexuses that will innervate the atria and ventricles: from the deep/dorsal cardiac plexus, the left coronary cardiac nerve (which runs along the left anterior descending coronary artery) and the left lateral cardiac nerve (which runs along the circumflex coronary artery) arise. From the ventral plexus, the right coronary cardiac nerve (which runs along the right coronary artery) arises (*Janes et al., 1986*). Additional cardiopulmonary nerves connect to these (coronary) cardiac nerves distal from the plexuses. Surprisingly, the left coronary cardiac nerve is composed mainly of contributions of right-sided cardiac nerves, largely originating from the right stellate ganglion, which pass through the deep (dorsal) cardiac plexus. The right coronary cardiac nerve is composed mainly of

contributions of left-sided cardiac nerves, largely originating from the left stellate ganglion, which pass through the superficial (ventral) cardiac plexus (*Janes et al., 1986; Table 3*).

Table 3: Summary of asymmetrical and regional features of the extrinsic cardiac plexus, coronary cardiac nerves, and intrinsic cardiac plexus (all human studies)

- Right-sided extrinsic cardiac plexus formation located more superiorly (level of brachiocephalic trunk) than left-sided extrinsic cardiac plexus (level of aortic arch) (*Kawashima, 2011*)
- Right coronary cardiac nerve: composed largely from contributions of left stellate ganglion (*Janes et al., 1986*)
- Left coronary cardiac nerve: composed largely from contributions of right stellate ganglion (*Janes et al., 1986*)
- Dorsal and ventral right atrial intrinsic cardiac plexuses: mainly parasympathetic (*Petraitiene et al., 2014*)
- Left and right coronary epicardiac plexuses: mainly sympathetic (*Petraitiene et al., 2014*)
- Predominance of parasympathetic neurons in plexuses on the atria (*Wake and Brack, 2016*)
- Predominance of sympathetic neurons in plexuses on the ventricles (*Wake and Brack, 2016*)

Intrinsic Cardiac Ganglia: Anatomical Evidence of Regional Organization and Gradient in (Para)Sympathetic Dominance (Figure 4)

Apart from nerves that conduct signals from the central nervous system to the human heart (i.e., extrinsic cardiac nerves), an intrinsic cardiac nervous system is also present. A network of over 800 ganglia can be found on the posterior surfaces of the atria, around the base of the aorta and pulmonary artery, dorsal and ventral to the pulmonary veins, and on the ventricular myocardium near the coronary arteries (*Singh et al., 1996; Armour et al., 1997; Pauza et al., 2000; Wake and Brack, 2016*). These ganglia are usually embedded in epicardial adipose tissue and are more or less organized into seven regions, called ganglionated (sub)plexuses: the right dorsal atrial plexus, the ventral right atrial plexus, the left dorsal plexus, the ventral left atrial plexus, the middle dorsal plexus, the right coronary plexus, and the left coronary plexus (*Pauza et al., 2000; Wake and Brack, 2016*). Nerve fibers in these plexuses are sympathetic, parasympathetic, or mixed. The dorsal and ventral right atrial ganglionated subplexuses (supplying also the sinoatrial node) are predominantly parasympathetic. The left and right coronary epicardiac subplexuses (supplying mostly the ventricles) are predominantly sympathetic (*Petraitiene et al., 2014; Table 3*). There is a predominance of parasympathetic neurons in plexuses on the atria and sympathetic neurons in plexuses on the ventricles (*Wake and Brack, 2016*). A considerable part of the intrinsic cardiac ganglion cells show co-expression of sympathetic and parasympathetic markers, as was shown in rhesus monkeys as well as humans (*Weihe et al., 2005*). This network has a function in passing down vagal impulses further and also in integrating sympathetic, parasympathetic, and sensory information in complex cardiac responses (*Armour et al., 1997; Hasan, 2013; Wake and Brack, 2016*).

Interestingly, in the experimental treatment of refractory vagally mediated reflex syncope, ablation of both left- and right atrial sites of parasympathetic innervation has shown promising results. Even though an anatomical substrate for these conditions may be difficult to locate, it appears that damaging parasympathetic control of the heart on either side may prevent recurring episodes (*Pachón et al., 2005; Sun et al., 2016*).

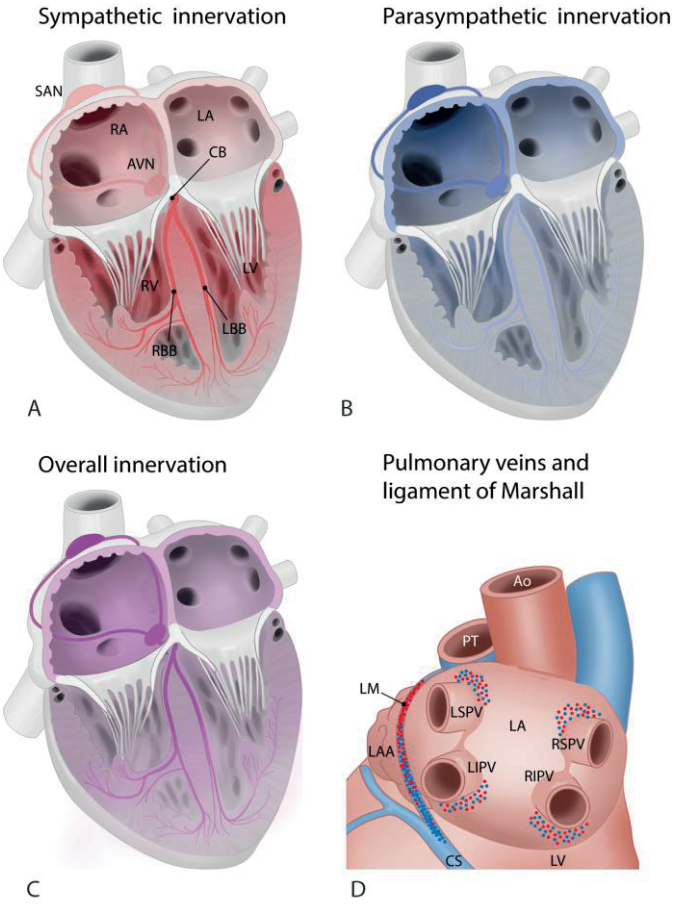

Figure 4: Innervation of the cardiac muscle, including the cardiac conduction system. *Red: sympathetic innervation, blue: parasympathetic innervation. (A,B) Schematic overview of sympathetic (A) and parasympathetic (B) innervation of the cardiac compartments and cardiac conduction system. Innervation gradient ranging from the most to least dense innervation: sinoatrial node > atrioventricular node > penetrating bundles > bundle branches. The conduction system is more densely innervated than surrounding myocardium. Sinoatrial node and atrioventricular node: predominantly parasympathetic innervation, penetrating bundle and the bundle branches: predominantly sympathetic (Crick et al., 1994; Chow et al., 2001). (C) Global innervation densities in cardiac areas. Innervation density in the atria > innervation density in the ventricles. Gradient in innervation density (higher to lower) from base to the apex. Atria: most nerve endings parasympathetic. Ventricles: most nerve endings sympathetic. Sympathetic innervation density right atrium > left atrium. Right atrium and right ventricle: higher density of parasympathetic innervation than left atrium and left ventricle (Kawano et al., 2003). (D) Innervation of the pulmonary veins and ligament of Marshall, posterior view of the left atrium. Sympathetic and parasympathetic innervation density: highest above superior pulmonary veins and below inferior pulmonary veins (Tan et al., 2006). The ligament of Marshall is densely sympathetically and parasympathetically innervated (Han et al., 2010; Rodríguez-Mañero et al., 2016). From superior to inferior, it shifts from predominantly sympathetic to predominantly parasympathetic. AVN, atrioventricular node; AVB, atrioventricular/His bundle; CB, common bundle; LA, left atrium; LBB, left bundle branch; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LV, left ventricle; SAN, sinoatrial node; RA, right atrium; RBB, right bundle branch; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; RV, right ventricle.*

Anatomical Evidence of Regional Differences in Cardiac Innervation Density: Sympathetic and Parasympathetic

Generally, in humans, innervation density is higher in the atria than in the ventricles, and a gradient in innervation density (higher to lower) is present from the ventricular base to the apex (*Kawano et al., 2003*). In the atria, most nerve endings are parasympathetic, and in the ventricles, most nerve endings are sympathetic (*Kawano et al., 2003*). The right atrium (RA) has a higher density of sympathetic innervation than the left atrium (LA) (*Kawano et al., 2003*). The RA and RV have a higher density of parasympathetic innervation than the LA and LV (*Kawano et al., 2003; Figure 4*).

Specifically in the human conduction system, there is an innervation gradient ranging from the most dense innervation in the sinoatrial node to less innervation in the atrioventricular node, penetrating bundles, and bundle branches (*Crick et al., 1994; Chow et al., 2001*). As a whole, the conduction system is more densely innervated than the atrial and ventricular myocardium (*Crick et al., 1994; Chow et al., 2001*). The normal adult conduction system is innervated by both sympathetic and parasympathetic nerve branches (*Crick et al., 1994; Chow et al., 2001*). The sinoatrial node and atrioventricular node predominantly show parasympathetic innervation, whereas the penetrating bundle and the bundle branches predominantly show sympathetic innervation (*Crick et al., 1994; Chow et al., 2001; Figures 4A,B*).

Interestingly, the innervation of the human conduction system changes considerably with age. In infants, more sympathetic nerves are present in all regions of the conduction system compared to parasympathetic nerves. During childhood and adulthood, the number of parasympathetic nerves increases to the extent that the levels of sympathetic and parasympathetic nerves are equalized. In the elderly, there is a decline in both types of nerves (*Chow et al., 2001*). These data implicate that the autonomic innervation of the human cardiac conduction system changes with age.

In the adult human LA, the area around the pulmonary veins is densely innervated (*Figure 4D*): many ganglionated plexuses with both sympathetic and parasympathetic fibers are found in this area. The right pulmonary veins are mostly innervated by the dorsal right atrial subplexus and the middle dorsal subplexus, whereas the left superior pulmonary vein is innervated by the left dorsal subplexus and the left inferior pulmonary vein is innervated by the left and middle dorsal subplexus (*Vaitkevicius et al., 2008, 2009; Wickramasinghe and Patel, 2013*). Sympathetic and parasympathetic innervation density are both especially high in the superior aspects of the superior pulmonary veins and the inferior aspects of the inferior pulmonary veins. Innervation density was also higher epicardially than endocardially (*Tan et al., 2006*). The pulmonary

venous myocardium is infamous for its potential for arrhythmogenesis (*Haïssaguerre et al., 1998*), and autonomic innervation has been recognized as a potential modulating factor (*Chen et al., 2014*). Of interest, the potential for arrhythmogenicity appears to differ between different pulmonary veins, with more foci found in the superior pulmonary veins as compared to the inferior veins (*Haïssaguerre et al., 1998; Chen et al., 1999*). Transient autonomic dysfunction and neural injury has been described after catheter ablation of pulmonary vein for atrial fibrillation (*Hsieh et al., 1999; Scherschel et al., 2019*). The ligament of Marshall, a remnant of the left vena cava inferior that regresses during embryonic development, is surrounded by a dense network of both sympathetic and parasympathetic fibers. From superior to inferior, in humans, the innervation of the ligament of Marshall shifts from predominantly sympathetic (nerve density) to predominantly parasympathetic (presence of parasympathetic ganglia) (*Makino et al., 2006; Han et al., 2010; Rodríguez-Mañero et al., 2016; Figure 4D*). The ligament of Marshall has nerve connections with the LA which are implicated in the genesis of atrial fibrillation (*Han et al., 2010*).

Animal studies reveal additional, potentially clinically relevant regional differences: in pigs, the RV was more densely innervated than the LV, whereas the left ventricular endocardium was more densely innervated than the right ventricular endocardium (*Ulphani et al., 2010*). In the RV outflow tract in dogs, sympathetic axons are found in the subendocardium as well as in the subepicardium, whereas in the remainder of the RV and the LV, sympathetic axons are only found in the subepicardium (*Ito and Zipes, 1994*), indicating a denser sympathetic innervation of the RV outflow tract as compared to the remainder of the RV. Whether this is also the case in humans is yet to be confirmed.

Sidedness and Regional Differences in Cardiac Sympathetic Receptors and Responses: Anatomical and Functional Evidence

In preganglionic sympathetic nerve terminals, acetylcholine is the primary neurotransmitter. In postganglionic sympathetic nerve terminals, norepinephrine (NE) is the neurotransmitter primarily involved. Postganglionic sympathetic nerve fibers activate adrenergic receptors (the α1-, β1-, and β2-adrenergic receptors, of which the β-receptors greatly outnumber the α-receptors). β1-receptors, the predominant receptors in the heart, outnumber the β2-receptors in the atria and even more so in the ventricles. As the total β-receptor density is similar in the myocardial walls of all four cardiac chambers (*Steinfath et al., 1992; Brodde et al., 2001*), differences in the ratio β1 versus β2 receptors may be present between atria and ventricle or within the different

cardiac compartments. Generally, stimulation of adrenergic receptors causes positive inotropy and an increase in heart rate. Though mostly present in the vascular wall, there are also α-adrenergic receptor in the ventricular myocardium, accounting for approximately 15% of the cardiac adrenergic receptors. Stimulation of the α1-myocardial receptors results in a weak positive inotropic response (*Bristow et al., 1988; Table 4*).

Table 4. Asymmetry and regional differences in the distribution and response of cardiac autonomic receptors and modulating factors

Autonomic division	Receptor or modulating factor	Cardiac distribution	Asymmetrical/regional features of action
Sympathetic	Adrenergic	β1-receptors > β2-receptors in all chambers (human tissue) β-receptors > α-receptors in all chambers (human tissue)	Relative increase in inotropy after β-stimulation RV > LV (dogs) Adrenergic stress may specifically lead to RVOT obstruction (dogs) α1-receptor stimulation: negative inotropy in RV, positive inotropy in LV (mice)
	NGF	NGF concentration ventricles > atria (rats) NGF concentration LA > RA (rats)	
Parasympathetic	Muscarinic	M2-receptor concentration atria > ventricles (human tissue) M2-receptor-specific tracer binding LV > RV > atria (human radioactive tracer imaging)	
	NOS	Expression eNOS left ventricular epicardium > RV > left ventricular endocardium (ferrets) Expression nNOS left ventricular endocardium > left ventricular epicardium and RV (ferrets)	

eNOS, endothelial nitric oxide synthase; LA, left atrium; LV, left ventricle; NGF, nerve growth factor; nNOS, neuronal nitric oxide synthase; NOS, nitric oxide synthase; RA, right atrium; RV, right ventricle.

Linked to differences in recruitability of the systemic and pulmonary vasculature, the LV and the RV show differences in responses to adrenergic stimulation. In athletes, it was shown that during exercise, there is a greater relative increase of wall stress in the RV compared with the LV (*La Gerche et al., 2011*). In dogs receiving sympathetic stimulation, a stronger increase in systolic pressure was seen in the RV compared with the LV. This is likely mediated by β-receptors, as it was not affected by α-receptor blockade (*Abe et al., 1987*). A more recent study in dogs showed similar results: a stronger relative increase of contractility was seen in the RV compared with the LV after β-stimulation, which appeared to be related to interventricular differences in phosphodiesterase metabolism underlying the response to β-stimulation (*Molina et al., 2014*).

Adrenergic stress, for example treatment with inotropes, can cause dynamic RV outflow tract obstruction in humans, even without right ventricular hypertrophy (*Denault et al., 2006*). A study in pigs shows that the RV outflow tract indeed demonstrates an augmented response to adrenergic stimulation compared to the inflow tract, which was suggested by the authors as a possible mechanism to prevent excessive blood flow to the pulmonary circulation (*Heerdt and Pleimann, 1996*). This may be related to the additional presence of sympathetic axons in the deep myocardium specifically in the RV outflow tract, as was demonstrated in dogs (*Ito and Zipes, 1994*).

Furthermore, animal research shows that the RV and the LV may differ in their responses to sympathetic stimulation. Ex vivo stimulation of the α1-receptor with phenylephrine in ventricular trabeculae in mice resulted in negative inotropy in the RV and in positive inotropy in the LV (*Wang et al., 2006*).

Nerve growth factor (NGF), an important factor in nerve (re)growth which likely acts on the p75 neurotrophin receptor and tropomyosin-related receptor A (*Li and Li, 2015*), was investigated in rats of different ages (*Saygili et al., 2012*). Across all ages, nerve growth factor expression was higher in the ventricles than in the atria, and higher in the LA than in the RA. In the atria, nerve growth factor expression increased with age. In the ventricles, nerve growth factor expression was highest in neonatal rats. It decreased from neonatal to young age, to increase again at old age. These results may be related with an increase in sympathetic activation with age (*Saygili et al., 2012*). It is unknown whether these patterns can be extrapolated to humans. Regional differences in nerve growth factor expression in the human heart have not yet been investigated.

An important regulator of cardiac beta-adrenoreceptor signaling is the opioid receptor system. Three subtypes of endogenous opioids exist, all three of which have effects on the heart through their specific receptors: the μ opioid receptor, δ opioid receptor, and κ opioid receptor (*Barron, 1999*). The cardiac opioid system may especially be important as part of a negative feedback loop: conditions such as exercise and hypertension lead to increased cardiac opioid content, which depresses neurotransmitter release at adrenergic and/or vagal nerve terminals. Distribution of these receptors appears to be asymmetrical in rat studies: more δ opiate receptors are present on the right side of the heart compared to the left, and more receptors are furthermore present in the atria compared to the ventricles (*Krumins et al., 1985*). Activity of endogenous opioids (enkephalins), the ligands for these receptors, was generally higher in the atria than in the ventricles in a study in guinea pigs (*Weihe et al., 1985*).

The asymmetry and regional differences in the distribution and response of cardiac sympathetic receptors and modulating factors are summarized in *Table 4*.

Asymmetry and Regional Differences in Cardiac Parasympathetic Receptors and Responses: Anatomical Evidence

Acetylcholine is the neurotransmitter employed in pre- and postganglionic parasympathetic nerve terminals. Postganglionic parasympathetic fibers mainly activate the muscarinic (M)2-cholinergic receptor. Stimulation of the M2-cholinergic receptor causes a negative inotropic effect and a decrease in heart rate (*Brodde et al., 2001*). An in vitro study in diseased human hearts showed a higher density of M2-receptors in the atria than in the ventricles (*Deighton et al., 1990; Table 4*). However, a radioactive tracer-imaging study in mainly healthy volunteers shows that the human LV and septum show the highest concentrations of the M2-receptor-specific tracer. Therefore, in physiological conditions the LV and septum may contain most of the physiologically active population of M2-receptors (*Syrota et al., 1985; Table 4*). In humans, the M2-receptor density decreases with age, as was shown by both functional evidence and in vitro study of the human RA (*Brodde et al., 1998*).

Nitric oxide (NO) plays an important role in parasympathetic regulation, as was demonstrated in animal models: under physiological circumstances, NO promotes acetylcholine release and reduces NE release from nerve terminals (*Herring and Paterson, 2001; Dedkova Elena et al., 2003*). Two different isoforms of nitric oxide synthase are primarily responsible for this: neuronal nitric oxide synthase (nNOS) in parasympathetic nerve terminals, and endothelial nitric oxide synthase (eNOS) in cardiac cells (*Balligand et al., 2009*).

From a clinical point of view, NO is implicated in vasovagal syncope: in young patients, this condition is mostly due to reduced systemic vascular resistance, which can be corrected by antagonizing NO (*Stewart et al., 2017*). In older patients, vasovagal syncope is mostly due to reduced cardiac output.

The distribution of NOS isoforms may be asymmetrical: in ferrets, eNOS expression is highest in the apical/midventricular epicardium of the LV, moderately high in the right ventricular free wall, and low in the left ventricular endocardium and the left ventricular side of the septum. In the sinoatrial node and the RA, eNOS is present in the majority of cells. The distribution of nNOS follows a more or less inverted pattern: the expression is high in the left ventricular endocardium and the left ventricular side of the septum, and low in the left ventricular epicardium and the RV (*Brahmajothi and Campbell, 1999*). The exact functional role and distribution of NOS isoforms in the human heart remains to be elucidated.

The asymmetry and regional differences in the distribution of cardiac parasympathetic receptors and modulating factors are summarized in *Table 4*.

Summary and Clinical Implications

In the current review, we show that the human peripheral cANS shows considerable asymmetry, interindividual variations, and regional differences in anatomical, functional and molecular characteristics.

The right-sided lower thoracic cardiac nerves follow a complex course to reach the heart which differs greatly from the course of the left-sided lower thoracic cardiac nerves. The presence of the left-sided thoracic cardiac branch is highly variable, the localization of the cardiac plexus is higher on the right side compared to the left, and different parts of the cardiac plexus give rise to nerves innervating different parts of the heart. This is important to consider when planning thoracic surgery to avoid complications regarding autonomic function.

The left and right stellate ganglia and the left and right vagus nerves innervate different areas of the heart or have different effects on the same area. In particular, left stellate ganglion block may be used to treat ventricular arrhythmias. The RV outflow tract, pulmonary veins, and the ligament of Marshall have specific innervation gradients. Distribution of cardiac nerves and ganglia differs between regions, showing a parasympathetic predominance in the atria and a sympathetic predominance in the ventricles. The distribution of spinal and vagal afferent nerve fibers may differ between

cardiac regions. The RV, the RV outflow tract, and the LV all respond differently to sympathetic stimulation. These factors heavily influence disease manifestation and efficacy of pharmaceutical treatment, and are therefore important to keep in mind. In addition, the risk of clinical procedures such as catheter ablation or stellate ganglion blockade for arrhythmias, may be reduced and their efficacy may be improved by taking asymmetry and regional differences of the cANS into consideration.

Many studies in this field are animal studies, and the RV is often neglected. Future research in human tissue or human subjects focusing for example on specific innervation of the RV outflow tract, distribution of cardiac afferents, regional differences in nerve growth factor or nitric oxide synthase expression, and differing effects of left- or right sided innervation on both the LV and the RV, would be highly valuable to comprehend the influence of cardiac innervation of disease course and potentially adjust treatments for specific cardiac diseases related to cardiac autonomic (dys)function.

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Chapter 3

Association between reduced heart rate variability components and supraventricular tachyarrhythmias in patients with a systemic right ventricle

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Abstract

Background

Patients with a systemic right ventricle are prone to develop heart failure. Abnormal heart rate variability (HRV), a measure of autonomic dysfunction, is associated with morbidity and mortality in patients with left ventricular failure. The association between HRV and supraventricular arrhythmias (SVTs), which are associated with adverse events in this population, was assessed.

Methods

24-Hour Holter recordings of patients with a systemic right ventricle and healthy controls were analysed in a retrospective cohort study. HRV was calculated and compared between groups. Correlation coefficients were determined for HRV variables and clinical characteristics. The relation between HRV and SVTs was investigated with linear regression.

Results

The patient group included 29 patients (69%) late after Mustard or Senning correction for transposition of the great arteries, and 13 patients with congenitally corrected transposition of the great arteries (31%). The control group included 38 subjects. HRV was significantly lower in patients compared with controls. In the patient group, lower SDANN (standard deviation of the average NN intervals calculated over 5-minute intervals) was independently associated with a higher number of supraventricular arrhythmias (95% CI −0.03 to −0.0004, p = 0.045). In exploratory correlation analysis, several HRV variables correlated with echocardiographic systemic right ventricular function (rho = 0.36, p = 0.02 for SDANN), and exercise capacity (rho = 0.39, p = 0.05 for SDANN).

Conclusion

In patients with a systemic right ventricle, HRV is lower compared with controls and (SDANN) is independently associated with supraventricular arrhythmias.

Introduction

Sympathetic and parasympathetic autonomic innervation of vital organs enable adaptation to external circumstances, allowing optimal functioning ranging from 'fight or flight' to 'rest and digest', respectively. However, autonomic nervous system responses to disease states may also eventually contribute to the pathophysiology. Sympathetic overstimulation accompanies left-sided heart failure from the onset, initially leading to restoration of cardiac output but ultimately leading to loss of inotropic reserve and increased susceptibility to arrhythmias (*Franciosi et al., 2017*). Parasympathetic activity is considered to have a protective effect against ventricular arrhythmias, but is often reduced in patients with heart failure (*Brack et al., 2013*).

Adult patients with congenital heart disease with a systemic right ventricle (RV) in a biventricular circulation, i.e. patients with transposition of the great arteries (TGA) after Mustard or Senning correction or patients with congenitally corrected TGA (ccTGA), are prone to develop heart failure and other complications, such as systemic atrioventricular valve regurgitation, impulse formation and conduction disorders, and tachyarrhythmias (*Brida et al., 2018*). Specifically, supraventricular tachyarrhythmias (SVTs) are very common: in patients after Mustard or Senning repair they may be caused by atrial scar tissue and in patients with ccTGA they are often caused by congenital accessory pathways (*Hernandez-Madrid et al., 2018*). SVTs appear to be predictive of mortality and sudden cardiac death in patients with a systemic right ventricle, with most evidence in the Mustard/Senning group (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

Cardiac autonomic function is disturbed in many congenital heart diseases. This may be a compensatory mechanism but can also be a consequence of surgery or of abnormal development. As autonomic function provides important prognostic information, data regarding autonomic function in systemic RV patients may be valuable in clinical practice.

Cardiac autonomic function can be assessed noninvasively with analysis of heart rate variability (HRV), which is a quantification of spontaneous fluctuations of heart rate. HRV analysis consists of time domain variables and frequency domain variables. Time domain variables quantify the amount of variability in all normal-to-normal (NN) interbeat intervals (excluding non-sinus beats) of a recording (for example a 5-minute electrocardiogram (ECG) or a 24-hour Holter recording). An example is SDNN (standard deviation of all normal-to-normal intervals). Frequency domain variables show how much of the total variance (=power) lies within certain predefined frequency bands.

Variations in heart rate follow many cyclic patterns. Some are known to be caused by autonomic modulation, others are caused by unknown factors. A clarifying example of a well-known cyclic pattern in heart rate is respiratory sinus arrhythmia (RSA). RSA, i.e. fluctuations in heart rate following the frequency of breathing, is caused by parasympathetic output to the sinus node. Parasympathetic stimulation of the sinus node leads to an increase in spontaneous fluctuations, especially on the short term. The frequency domain parameter high-frequency (HF) power, which describes distribution of heart rate variance across the frequency of 0.15–0.4 Hz, which includes breathing frequency, is therefore largely ascribed to vagal modulation (*Akselrod et al., 1981*).

Generally, considerable variation in heart rate is a sign of health and decreased HRV is a sign of disease. In healthy, resting humans, parasympathetic tone predominates. A predominating sympathetic tone, however, leads to a decrease in the time-domain variables of HRV. Regarding frequency domain variables, both sympathetic and parasympathetic influences modulate a part of the low-frequency (LF) power, but other and unknown factors also influence this peak, therefore the exact composition of the LF peak is unclear (*Camm et al., 1996*).

Several studies (for example (*La Rovere et al., 1998*)) have demonstrated decreased HRV in patients with congestive heart failure, which is an independent risk factor for mortality in this group. Most data are derived from studies in patients with left ventricular (LV) failure based on ischemic or non-ischemic cardiomyopathy. Recently, it has become clear that autonomic dysfunction also plays an important role in diseases involving primarily RV dysfunction. For example, in patients with pulmonary hypertension, HRV is decreased and correlated with disease progression (*Bienias et al., 2015*). In (young) adult patients late after repair of tetralogy of Fallot, abnormal HRV is correlated with pulmonary valve regurgitation and with the number of years after repair (*Davos et al., 2002*). Importantly, abnormal HRV patterns are also associated with ventricular arrhythmias and sudden cardiac death, both in left ventricular (LV) and RV disease (*Davos et al., 2002; Valkama et al., 1995*).

The aims of the current study were to gain insight in the patterns of autonomic (dys) function of the systemic RV and to study whether HRV is correlated with SVTs in this group, as SVTs are an important marker of clinical status and may provide indirect information about clinical outcome. We hypothesised that worse HRV would be associated with SVTs and other clinical characteristics reflective of cardiac deterioration, such as exercise capacity and echocardiographic systemic RV function.

Methods

Design

A retrospective cohort study was performed. HRV analysis was carried out in systemic RV patients and healthy controls. Correlation of HRV with clinical factors was investigated. The need for informed consent was waived by the Leiden University Medical Center's medical ethical committee. The study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki.

Selection of patients and controls

All files of adult patients with a systemic RV and a biventricular circulation under current/past follow-up in our center were screened for the presence of digitally available 24-hour Holter registrations. A control group was formed by consecutive patients referred for cardiac screening because of possible genetic cardiac abnormalities. As part of the screening protocol, 24-hour Holter monitoring, echocardiography, genetic testing, and (bicycle) exercise test were conducted. Control subjects were eligible for inclusion if no genetic abnormalities and no abnormalities in the cardiac investigations were found. For both patients and controls, protocols for the exercise tests are in accordance with the guidelines of the American College of Cardiology/American Heart Association (*Fletcher et al., 2013*).

Exclusion criteria

Patients or controls were excluded if there were no available/interpretable Holter monitoring records. Holter recordings were excluded if the primary rhythm was not sinus rhythm or if the quality was insufficient, if the patient had clinically relevant diabetes (defined as the use of at least one antidiabetic drug), had rheumatoid arthritis, or was using antidepressant or antipsychotic medication, due to potential interference with cardiac autonomic function (*Benichou et al., 2018; Koopman et al., 2016; O'Regan et al., 2015*). Control subjects were excluded if they had a history of relevant cardiac disease, or if they were using β-blockers.

Holter processing and variables

For each patient or control subject, the most recent 24-hour Holter registrations were analysed. Processing and HRV calculations were performed with the specialised program MARS, version 8 (GE Healthcare, Milwaukee, United States). In line with standard HRV settings in MARS, RR interval ratios <0.8 and >1.2 (probably indicating a sinus pause or an ectopic beat) were automatically excluded. RR intervals >1500 ms (40 beats per minute) were also automatically excluded because this amount of bradycardia affects HRV calculation and is furthermore more likely to be ectopic atrial

rhythm or a consequence of sinus node dysfunction rather than autonomic modulation. Registrations were thoroughly manually reviewed for correct labelling and correct onset of the QRS-complexes. Episodes with non-sinus ectopic atrial rhythm or unreliable signals were excluded. The rhythm was considered to be sinus rhythm in cases with positive p-waves on Holter lead II and III. This was always confirmed with 12-lead ECGs. In all cases, consensus was reached by discussion with experienced congenital cardiologists (HV, PK, AE, MJ). Registrations with <18 h of analysable time (due to either noise or large proportion of non-sinus rhythm) were excluded, in accordance with HRV guidelines (*Camm et al., 1996*). All in all, Holters from patients with sick sinus syndrome, or the parts of the Holters displaying these features, were likely to be excluded. Therefore, sick sinus syndrome was not analysed in the context of HRV in this study.

The HRV function in MARS was used for calculation of the following variables: SDNN (standard deviation of all normal-to-normal, or NN intervals), SDANN (standard deviation of the average NN intervals calculated of all 5-minute intervals), ASDNN (average standard deviation of all NN intervals for all 5-minute intervals, pNN50 (percentage of adjacent NN intervals that differ by >50 milliseconds), rMSSD (square root of the mean squared differences of successive NN intervals)), (time domain), VLF (very low-frequency power, 0.003–0.04 Hz), LF (low-frequency power, 0.04–0.15 Hz), and HF (high-frequency power, 0.15–0.4 Hz) (frequency domain) (*Camm et al., 1996*).

Clinical characteristics and outcomes

For each patient or control, length, weight, body surface area (BSA), medication use, and age at the time of the Holter registration were noted. Values of N-terminal brain natriuretic peptide (NT-pro-BNP) and results of exercise tests closest to the time of Holter registration were noted when available, including: the number of maximum achieved Watts, exercise capacity (percentage of the predicted number of Watts), and the percentage of the predicted maximum heart rate (220-age) that was achieved. The global systemic RV function as noted in the report by the supervising imaging cardiologist was scored. Global longitudinal strain of the systemic ventricle was assessed offline in the apical four-chamber view (*Rudski et al., 2010*). Echocardiograms had been obtained with commercially available ultrasound systems and offline analysis was performed in EchoPac, GE Medical Systems.

To examine the role that HRV plays in current clinical context, a surrogate endpoint was constructed in the form of the number of supraventricular arrhythmias (SVTs) which occurred up until the time of the Holter recording. This methodology was chosen because assessment of the predictive power of HRV in the context of sudden cardiac

death or mortality was not feasible, and because SVTs are an important marker of clinical condition in patients with a systemic right ventricle (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*). SVTs were scored when they led to initiation of treatment or when they were persistent and accepted. So for example, an episode of atrial flutter was counted when it was followed by a change in anti-arrhythmic medication, but several episodes of paroxysmal flutter in a short period of time which were not treated, were not counted.

Statistical analysis

All statistical analyses were performed with IBM SPSS statistics version 23. Normally distributed data are reported as mean ± SD and non-normally distributed data are reported as median and interquartile range (IQR). For the comparison of baseline characteristics and Holter variables between patients and controls, a t-test or Mann-Whitney-U for independent samples was used for continuous data and the Chi-square or Fisher's exact test were used for categorical data, as appropriate. To assess correlations of clinical factors with HRV, Spearman's rho correlation coefficient was calculated. For all analyses, p-values<0.05 were considered statistically significant. Spearman's rho correlation coefficient was also calculated for clinical characteristics and HRV variables in the control group. Holm's correction method for multiple comparisons (*Holm, 1979*) was applied to the correlation analyses. In this method, the p-values are sorted smallest to largest and ranked accordingly. All raw p-values are then compared to 0.05*(number of tests-rank+1). If the raw p-value is smaller than the newly calculated threshold, the hypothesis can be accepted. If larger, it is rejected.

To assess whether HRV was associated with clinical outcome, linear regression was performed with the number of SVTs which occurred up until the Holter recording as outcome variable. Predictor variables were selected as follows: All HRV variables which had a statistically significant Spearman's correlation coefficient with the number of SVTs were included in the univariate analysis. Other clinical factors were also included when they were expected to be potentially clinically relevant. The multivariate model was constructed with stepwise forward addition of variables, starting with the most significant variables in univariate analysis. Addition of variables was terminated after addition of the last variable that improved the model significantly.

Results

Subjects and baseline characteristics

Holter recordings were analysed for 42 systemic RV patients (*Figure 1*) and 38 healthy controls. Both groups were comparable in terms of age and gender. Patients had worse exercise capacity, reduced chronotropic competence, and reduced systemic ventricular function (*Table 1*).

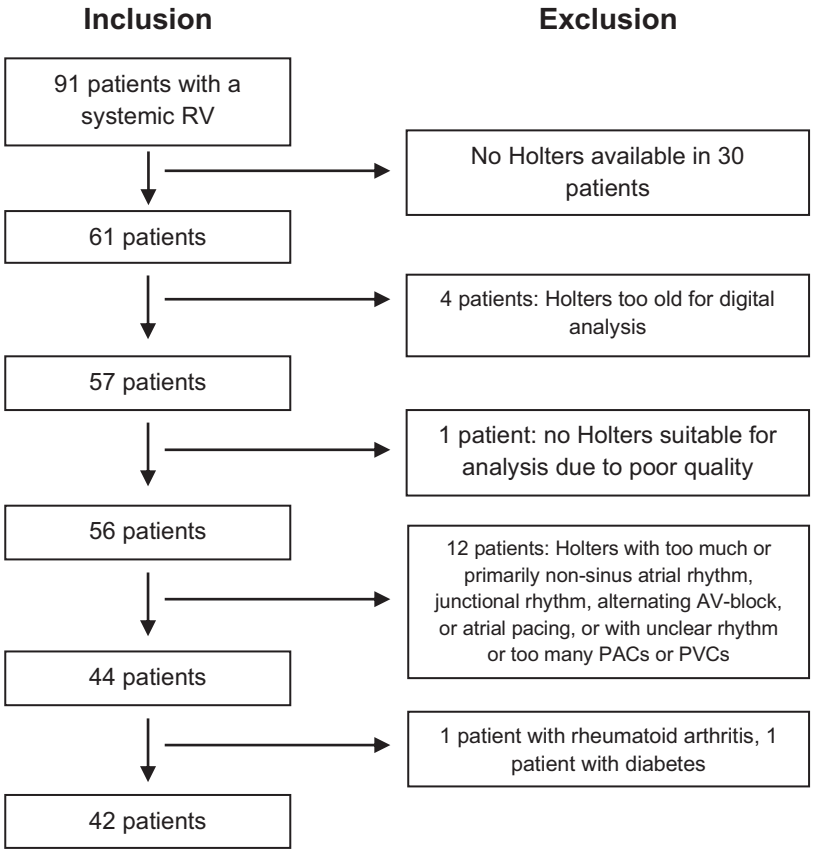

Figure 1: Flowchart patient Holter selection.
PACs: premature atrial complexes; PVCs: premature ventricular complexes; RV: right ventricle

Table 1: Baseline characteristics patients (at most recent Holter) and controls

Characteristics	Patients N (%)		Mean (±SD) or median (IQR)		Controls N (%)		Mean (±SD) or median (IQR)		p-value
Total number	42	(100%)			38	(100%)			
Females	18	(43%)			21	(55%)			0.27
Alive	40	(95%)			38	(100%)			0.50
Primary condition:									
Mustard	11	(26%)			n.a.				
Senning	18	(43%)			n.a.				
ccTGA	13	(31%)			n.a.				
Age (years)			40	(±9.5)			42	(±12.9)	0.49
BSA (m^2)			2.0	(±0.19)			1.9	(±0.23)	0.15
Holters per patient			2.0	(1.0–4.0)	1				
Patients with > 1 Holter	29	(69%)			0				
Time first-last Holter (years)			3.3	(0.0-8.4)					
Medication use:									
Beta-blocker	7	(17%)			0	(0%)			**0.01***
ACEi or ARB	18	(43%)			1	(3%)			**<0.01***
Diuretic	10	(24%)			1	(3%)			**0.01***
Bm/AC	2	(5%)			5	(13%)			0.24
Digoxin	1	(2%)			0	(0%)			1.00
Amiodarone	2	(5%)			0	(0%)			0.50
Class I anti-arrhythmic drug	2	(5%)			0	(0%)			0.50
Watts			160	(110-200)			200	(160-240)	**0.05***
Exercise capacity (%)			92	(80-115)			123	(±108-142)	**<0.01***
% of predicted heart rate			87	(±17)			97	(±7)	**0.011***
Systemic ventricular GLS[1]			14.7	(±2.3)			20.1	(±2.8)	**<0.01***
Systemic ventricular function[1]									**<0.01***
good (1)	1	(3%)			36	(97%)			
mildly reduced (2)	29	(72%)			1	(3%)			
moderately reduced (3)	10	(25%)			0	(0.0%)			
severely reduced (4)	0	(0.0%)			0	(0.0%)			
TR grade									**<0.01***
1 or less	20	(48%)			38	(100%)			
2	22	(52%)			0	(0%)			
3	0	(0%)			0	(0%)			
4	0	(0%)			0	(0%)			
Number of previous surgeries									**<0.01***
0	9	(21%)			38	(100%)			
1	16	(38%)			0	(0%)			
2	13	(31%)			0	(0%)			
3	4	(10%)			0	(0%)			

**Significant p value; 1: no echo available in 2 patients and in 1 control; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor antagonist; Bm/Ac: betamimetic or anticholinergic drug; BSA: body surface area; ccTGA: congenitally corrected transposition of the great arteries; GLS: global longitudinal strain; IQR: interquartile range; SD: standard deviation; TR: tricuspid regurgitation*

Comparison of HRV between patients and controls

Table 2 shows ECG characteristics and HRV data of patients compared with controls. Patients often had a right axis deviation of the QRS complex, and had significantly longer PR intervals, QRS durations, and QTc intervals compared with controls. SDNN, SDANN, and LF power were significantly reduced in the patient group. *Figure 2* shows SDNN and SDANN in patients and controls.

Table 2. Comparison ECG and Holter data between patients and controls

ECG	Patients (n=42) Mean±SD or median (IQR)		Controls (n=38) Mean±SD or median (IQR)		p value
Axis[1] (N, %)					**<0.01***
Normal	8	(21%)	33	(87%)	
Right axis deviation	20	(51%)	1	(3%)	
Left axis deviation	6	(15%)	4	(10%)	
Extreme axis deviation	5	(13%)	0	(0%)	
PR interval	184	±36	153	±21	**<0.01***
QRS[1] duration	113	(103 – 121)	100	(90 – 111)	**<0.01***
RBTB[1] (N, %)	8	(21%)	3	(8%)	0.19
LBTB[1] (N, %)	3	(8%)	1	(3%)	0.62
QTc interval[1]	423	±25	399	±17	**<0.01***
Holter					
Mean HR	72	(±7)	75	(±9)	0.07
SDNN (ms)	139	(±46)	161	(±36)	**0.02***
SDANN (ms)	122	(±44)	144	(±32)	**0.02***
ASDNN (ms)	59	(±20)	66	(±22)	0.13
pNN50 (%)	9.4	(6.2 – 14.8)	9.8	(4.3 – 19.0)	0.81
rMSSD (ms)	33	(27-42)	34	(25-44)	0.87
VLF (ms^2)	1072	(540-1290)	1140	(778-1776)	0.13
LF (ms^2)	383	(234-757)	669	(425-1164)	**0.01***
HF (ms^2)	165	(99-313)	199	(103-385)	0.53

**Significant p value; 1: 3 patients with ventricular pacing not included; ASDNN: average standard deviation of all NN intervals for all 5-minute intervals; HF: high-frequency power: HR: heart rate; IQR: interquartile range; LBTB: left bundle branch block morphology; LF: low-frequency power; ms: milliseconds; PAC: premature atrial complex; pNN50: percentage of adjacent NN intervals that differ by more than 50 ms; PVC: premature ventricular complex; QTc; heart rate corrected QT interval; RBTB: right bundle branch block morphology; rMSSD: square root of the mean squared differences of successive NN intervals; SD: standard deviation; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal (NN) intervals; VLF: very low-frequency power*

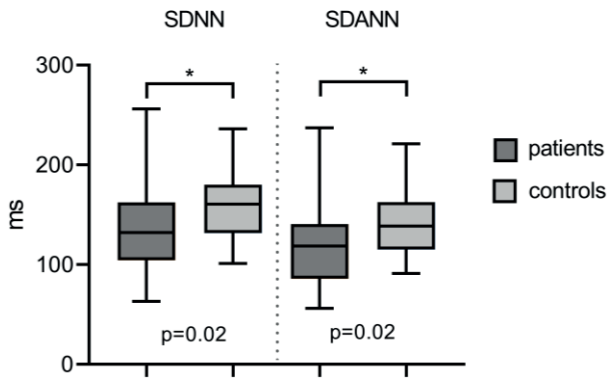

Figure 2: SDNN and SDANN in patients and controls.
SDANN: standard deviation of the average normal-to-normal (NN) intervals calculated over 5-minute intervals; SDNN: standard deviation of all NN intervals.

Correlation between HRV and clinical factors

Spearman's rho correlation coefficient was calculated to assess the correlation between the HRV variables and clinical factors, including the number of SVTs (*Table 3*). Higher age, worse echocardiographic RV function (higher GLS) (*Figure 3*), worse exercise capacity, and a higher number of SVTs correlated with lower HRV in several variables. The percentage of predicted maximum heart rate that was reached during exercise testing positively correlated with LF power. Higher exercise capacity correlated with higher HRV. NT-pro-BNP is not listed as very few values were available. After correction of the p-values according to Holm's method, only the correlations between SDNN and SVTs and SDANN and SVTs remained significant ($p=0.00033 <$ calculated norm of 0.00063, and $p=0.00024 <$ calculated norm of 0.00063, respectively).

Table 3: Correlations between HRV and clinical factors in most recent patient Holters

		SDNN	SDANN	ASDNN	pNN50	rMSSD	VLF	LF	HF
Age	rho	-0.34	-0.35	-0.26	-0.04	-0.07	-0.34	-0.28	-0.20
	p	**0.03***	**0.02***	0.10	0.81	0.66	**0.03***	0.07	0.22
Gender	rho	-0.03	-0.04	-0.01	0.11	0.08	-0.04	0.00	0.17
	p	0.85	0.79	0.93	0.49	0.64	0.78	0.98	0.28
Thoracotomies[a]	rho	-0.16	-0.16	-0.07	-0.12	-0.11	-0.08	-0.21	-0.24
	p	0.33	0.34	0.66	0.46	0.52	0.64	0.21	0.14
β-blocker use	rho	-0.24	-0.30	0.01	0.07	0.08	-0.08	0.01	0.09
	p	0.13	0.06	0.96	0.64	0.60	0.63	0.93	0.58
QRS duration	rho	0.14	-0.14	-0.09	0.14	0.14	-0.23	-0.06	-0.01
	p	0.40	0.40	0.58	0.39	0.40	0.17	0.70	0.96
QTc duration	rho	-0.14	-0.18	-0.04	0.21	0.20	-0.22	-0.02	0.04
	p	0.40	0.28	0.83	0.19	0.23	0.18	0.88	0.79
% of predicted	rho	0.11	0.04	0.27	-0.16	-0.06	0.27	**0.47**	0.08
heart rate[b]	p	0.63	0.85	0.25	0.51	0.80	0.25	**0.04***	0.73
Watts	rho	0.49	0.50	0.15	-0.41	-0.31	0.23	0.23	-0.25
	p	**0.01***	**0.01***	0.47	**0.04***	0.12	0.28	0.27	0.24
RV GLS	rho	-0.49	-0.50	-0.29	-0.04	-0.06	-0.43	-0.34	-0.08
	p	**<0.01***	**<0.01***	0.07	0.82	0.70	**<0.01***	**0.04***	0.62
SVTs	rho	**-0.53**	**-0.54**	-0.28	-0.02	-0.03	**-0.39**	**-0.31**	-0.13
	p	**<0.01***	**<0.01***	0.07	0.88	0.85	**0.01***	**0.05***	0.40

*ASDNN: average standard deviation of all NN intervals for all 5-minute intervals; HF: high-frequency power; LF: low-frequency power; pNN50: percentage of adjacent NN intervals that differ by >50 ms; rMSSD: square root of the mean squared differences of successive NN intervals; RV GLS: (systemic) right ventricular global longitudinal strain; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal (NN) intervals; VLF: very low-frequency power. *Significant p-value; a: excluding patients who underwent TVP/TVR; b: excluding β=blocker users*

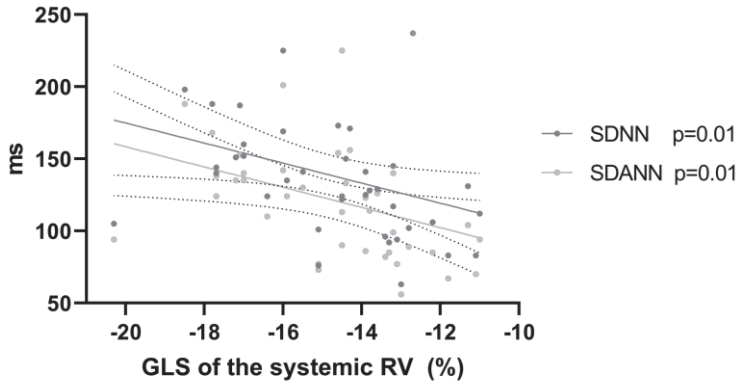

Figure 3: SDNN/SDANN and GLS of the systemic RV.
SDANN: standard deviation of the average normal-to-normal (NN) intervals calculated over 5-minute intervals; SDNN: standard deviation of all NN intervals; GLS: global longitudinal strain.

Linear regression: association between HRV and SVTs

Regression analyses with SVTs as the outcome variable are shown in *Table 4*. As SDNN, SDANN, VLF, and LF correlated with SVTs (*Table 3*), they were assessed in univariate linear regression (*Table 4*). Other potentially clinically relevant variables were also assessed. SDNN and SDANN were significantly associated with SVTs in univariate analysis, as were the number of Watts derived from bicycle exercise testing, the echocardiographic systemic RV GLS, the QTc interval, and β-blocker use. In multivariate analysis, only SDANN and the systemic RV GLS were independently associated with SVTs (*Table 4*). The percentage of predicted heart rate was not significantly associated with SVTs. However, chronotropic incompetence may affect HRV and therefore theoretically its association with SVTs, and the percentage of predicted heart rate is highly dependent on β-blocker use. Therefore, to explore these associations, another multivariate model was composed with SVTs as the outcome variable and the percentage of predicted heart rate, β-blocker use, and SDANN as predictor variables. Thus correcting for chronotropic incompetence and β-blocker use, SDANN remained significantly associated with SVTs (estimate −0.02, 95% CI −0.04 to −0.003, p = 0.025). The percentage of predicted heart rate and β-blocker were not significantly associated with SVTs in this model (data not shown).

Table 4. Determinants of SVTs in systemic RV patients.

Linear regression variable	Estimate univariate (95% CI)	p-value univariate	Estimate multivariate (95% CI)	p-value multivariate
Watts	−0.02 (−0.03 to −0.002)	0.033*		NS
% of predicted heart rate	−0.04 (−0.09–0.01)	0.079		NS
RV GLS	0.58 (0.29–0.88)	<0.001*	0.47 (0.17–0.77)	0.03*
SDNN	−0.02 (−0.03 to −0.004)	0.015*		NS
SDANN	−0.02 (−0.04 to −0.01)	0.009*	−0.02 (−0.03 to −0.0004)	0.045*
VLF	−0.001 (−0.002–0.000)	0.105		
LF	−0.001 (−0.002–0.001)	0.492		
QRS duration	0.03 (−0.004–0.06)	0.080		NS
QTc interval	0.03 (0.004–0.06)	0.028*		NS
β-Blocker use	2.03 (0.20–3.86)	0.031*		NS

*CI: confidence interval; LF: low-frequency power; NS: not significant; RV GLS: (systemic) right ventricular global longitudinal strain; SDANN: standard deviation of the average NN intervals calculated over 5-minute intervals; SDNN: standard deviation of all normal-to-normal intervals; VLF: very low-frequency power; QTc interval: corrected QT interval. *Significant p-value.*

Discussion

The current results show that HRV differs between patients with a systemic RV and controls, and is related to clinical factors in the patient group. SDANN was independently associated with SVTs. This is clinically relevant as SVTs are independently associated with sudden cardiac death and mortality in patients with a systemic RV (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

Next to the association between SDANN and SVTs, multiple time- and frequency domain variables of HRV correlated with SVTs, which were common in this cohort. They are usually attributed to scar tissue after Mustard or Senning procedures or macro-re-entrant circuits (*Hernandez-Madrid et al., 2018*). SVTs may furthermore be due to dilated atria because of tricuspid valve regurgitation, or re-entrant tachycardias through congenital accessory bundles in ccTGA patients (*Andrade et al., 2020; Daliento et al., 1986*). However, a disbalance between sympathetic and parasympathetic influence, as indicated by a change in HRV, can also be a trigger for SVTs (*Carnagarin et al., 2019*). SVTs predispose to heart failure and mortality through inducing tachycardiomyopathy and contributing to ischemia and are therefore an important clinical marker in patients with a systemic RV (*Connelly et al., 1996; Mongeon et al., 2011; Venkatesh et al., 2019*).

In this study, patients showed reduced SDNN, SDANN, and LF power compared with controls. These variables, together with VLF power, also appeared to be correlated with echocardiographic systemic RV function and with SVTs. These components of HRV reflect a mix of sympathetic, parasympathetic, and baroreflex activity. Variables known from previous evidence to primarily reflect parasympathetic activity, namely pNN50 and rMSSD, did not differ between patients and controls and did not correlate with clinical events. These results are striking, since heart failure is generally characterized by increased sympathetic activity and decreased parasympathetic activity.

Previously (*Malik and Camm, 1993*), it was pointed out that when either sympathetic or parasympathetic activity increases within the physiological range, their corresponding HRV components increase. However, when they are pathologically increased, for example in the case of sympathetic hyperactivity in heart failure, the sinus node may be saturated with sympathetic input and thus may not respond to the other sources of modulation anymore, leading to a decrease in sympathetically mediated HRV components.

The current cohort shows relatively preserved systemic RV function and relatively few heart failure related events, and thus likely represents a group of patients in a compensated state of (pre-)heart failure. Acute pathological sympathetic activity such as has been demonstrated in patients admitted with decompensated heart failure was very rare in this group, and Holter monitoring was usually conducted in steady states. However, the systemic RV is not equally equipped compared to the systemic LV to provide systemic pressure, and therefore, it is possible that the hearts of the current cohort have already been functioning under increased sympathetic stimulation since birth. From current literature it is as of yet unknown how such a pattern of autonomic activity reflects in HRV but a possible explanation of the presented findings may be that this activity also provides saturating sympathetic outflow to the sinus node.

A pattern similar to our findings was seen by Patel et al. in a group of healthy individuals with normal cardiac anatomy that would later develop heart failure (*Patel et al., 2017*): they demonstrated a.o. reduced SDNN, SDANN, LF power, and normal or even slightly increased measures of parasympathetic activity (rMSSD and HF power). This study indicates that our findings may indeed be reflective of a state of compensated (pre-)heart failure.

In the current cohort, a higher number of previous thoracotomies and therefore potentially a higher risk of surgical denervation, was not correlated with any of the studied HRV variables. This is in line with previous investigations: although thoracic

surgery may damage autonomic pathways to and from the heart on the short term, it has been demonstrated that full recovery usually takes place in a matter of months (*Kiseleva et al., 2002*). Furthermore, contrary to the arterial switch procedure (*Kondo et al., 1998*), during the Mustard or Senning procedures, the cardiopulmonary nerves coursing along the origin of the great arteries are not likely to be transsected as the great arteries are left intact.

The percentage of predicted heart rate that was achieved during exercise testing was positively correlated with LF power (only before p-value correction, however). This is in line with previous literature, showing a decreased LF power in the presence of chronotropic incompetence (*Fei et al., 1996*). However, the percentage of predicted heart rate did not affect the association between SDANN and SVTs. This suggests that, regardless of chronotropic (in)competence, HRV may still provide useful information about SVTs.

Study limitations

The current study was limited by its retrospective design, the limited patient numbers, and the heterogeneous population in which for example differing surgical factors may have influenced HRV. Also, it is unknown how HRV changes over time in relation to clinical events in this patient group. Therefore, the usefulness of HRV analysis in the individual patient still has to be confirmed by longitudinal studies in systemic RV patients. Studies with devices measuring HRV in patients with a structurally normal heart and heart failure are promising: a decline in HRV was observed in patients who progress from stable to unstable heart failure and the need for hospitalization (*Adamson, 2009*). Whether HRV can predict sudden cardiac death or mortality in patients with a systemic RV remains to be investigated, as the current limited sample size and limited number of events did not allow this. However, within the published studies regarding HRV in populations with specific complex congenital heart disease, this is one of the largest cohorts of adult patients. Most literature concerns either (mostly) children or consists of a heterogeneous group with different types of congenital heart disease (*Massin and von Bernuth, 1998; McLeod et al., 1999*).

HRV analysis requires sinus rhythm causing a selection bias since patients with overt sick sinus syndrome were excluded. Theoretically, it is possible that preclinical sinus node dysfunction affected the HRV in more subtle ways that did not lead to exclusion of the recording or the patient. Therefore, sinus node dysfunction may have influenced the current results to some extent. However, as sick sinus syndrome probably leads to an increase in HRV (pNN50, rMSSD, and SDNN) (*Butta et al., 2019*), the finding of a

decreased SDNN and LF power in the current cohort is probably unrelated to sinus node dysfunction and can be attributed to heart failure.

After Holm's correction of the p-values for the correlation coefficients between HRV variables and clinical factors (*Table 3*), only the association between SDNN/SVTs and SDANN/SVTs remained significant. However, pre-correction, there were more significant correlations (15) than would be expected purely by chance with a p-value cut-off of 0.05 (about 4, i.e. 1 in 20). Therefore, although the results need to be interpreted with caution, it might be too rigorous to reject all other correlations in *Table 3* besides SDNN/SVTs and SDANN/SVTs. It could be appropriate to use such results to guide formation of new hypotheses and the design of further studies (Perneger, 1998; Rothman, 1990).

Conclusion

In conclusion, HRV is associated with clinical factors and events in patients with a systemic RV. HRV analysis in this population may be useful to detect disease progression before this is clinically overt, and may provide indirect information about outcome. Further longitudinal research is needed.

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Chapter 4

QT interval variability and heart rate turbulence are associated with clinical characteristics in congenital heart disease patients with a systemic right ventricle

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Abstract

Background

QT interval variability (QTV) and heart rate turbulence (HRT) are measures of cardiac autonomic function, which, when abnormal, are correlated with ventricular arrhythmias and worse clinical outcome. This study aims to evaluate QTV and HRT in patients with a systemic right ventricle (RV) and to assess correlations with clinical characteristics.

Methods

In a retrospective cohort study, QTV and HRT were derived from 24-h Holter registrations of patients with a systemic RV and healthy controls. QTV and HRT were compared between groups. In patients, the association between QTV, HRT, and clinical characteristics was assessed.

Results

Holter recordings from 40 patients (mean age 40 years, 16 females) and 37 healthy controls (mean age 42 years, 21 females) were analyzed. Groups were comparable in terms of age and sex. QTV was increased in patients compared with controls ($p < 0.001$), HRT did not differ significantly between the groups. Increased QTV and decreased HRT correlated with medication use, especially of diuretics, and with clinical events, particularly supraventricular arrhythmias. Increased QTV correlated with reduced systemic RV function. Decreased HRT was independently associated with a larger number of past clinical events (estimate −0.33, 95% CI −0.63 to −0.02, $p = 0.037$). QTV was higher in women in both patients and controls ($p = 0.041$ and $p = 0.034$, respectively).

Conclusions

QTV and HRT are associated with clinical factors and events in patients with a systemic RV. Further studies are mandatory to confirm their prognostic value.

Introduction

Patients with congenital heart disease and a systemic right ventricle (RV) have a good mid-term prognosis but long-term complications are frequent, including heart failure and arrhythmias (both supraventricular and ventricular) [1]. The onset of clinical deterioration and the occurrence of complications are hard to predict. In patients with left ventricular disease, non-invasive measures of cardiac autonomic function have potential for use in risk stratification. Abnormal QT interval variability (QTV) and abnormal heart rate turbulence (HRT) are associated with decreased functional capacity, and are predictive of supraventricular and ventricular arrhythmias and mortality [2-8]. Data regarding QTV and HRT in patients with a systemic RV are however lacking.

The duration of the QT interval fluctuates with changes in heart rate, but also spontaneously, independent of heart rate. QTV describes these spontaneous fluctuations. Increased QTV indicates unstable ventricular repolarization and is thus considered to indicate a higher risk for ventricular arrhythmias [9]. Increased QTV may be caused by sympathetic overactivity [10], which can occur as a response to decreased cardiac output in congestive heart failure [4]. Increased QTV is associated with mortality, ventricular tachycardia/fibrillation (VT/VF), and atrial fibrillation in patients with left-sided cardiac disease [2-4].

HRT describes the pattern of acceleration and deceleration of heart rate after a premature ventricular complex (PVC). The transient drop in blood pressure caused by a PVC causes quick parasympathetic withdrawal through activation of the baroreflex. The sympathetic nervous system is activated but with a slight delay. Both mechanisms increase heart rate and blood pressure. The increased blood pressure is registered by the baroreceptors and heart rate is subsequently reduced. In the healthy individual, this response generates an overshoot in both the increase and subsequent decrease in heart rate, which leads to a clear HRT pattern (*Fig. 1*). Normal HRT thus reflects good baroreflex sensitivity, which is an important manifestation of intact parasympathetic function [11]. In patients with left-sided cardiac disease, decreased HRT is associated with mortality, VT/VF, and atrial fibrillation [6-8]. In patients after myocardial infarction, decreased HRT was independently associated with mortality [12] and in patients with operated or unoperated congenital heart disease, HRT was the strongest independent predictor of sudden cardiac death [13]. In the present study, we investigated QTV and HRT in adult patients with a systemic RV and explored the association between QTV and HRT and clinical characteristics and outcomes in this group.

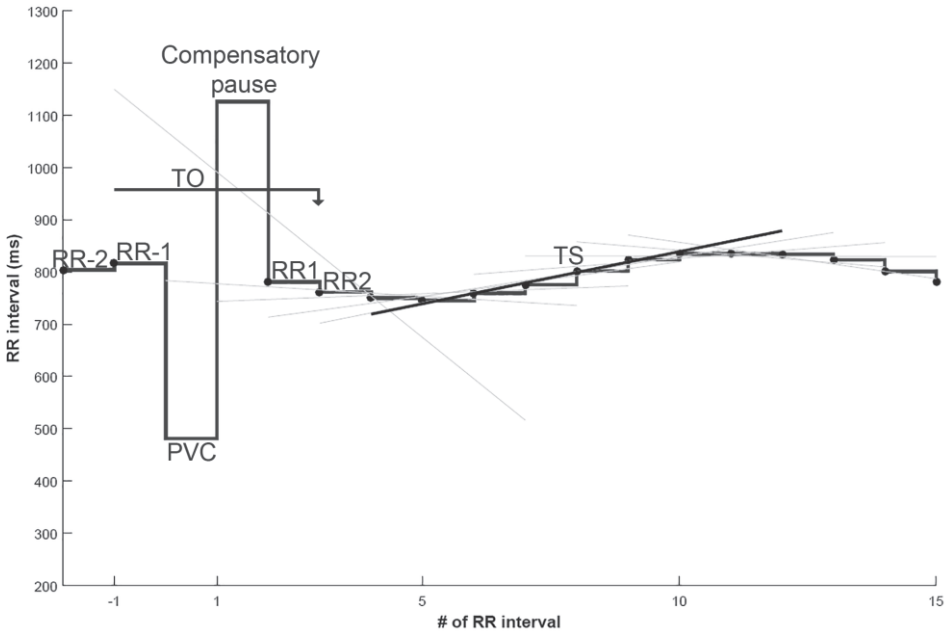

Figure 1. Representative example of heart rate turbulence calculation in a control subject.
PVC, premature ventricular complex; RR-1 and RR-2, the two sinus beats preceding the PVC; RR1 and RR2, the two sinus beats following the PVC; TO, turbulence onset, the percentage of difference between the mean RR intervals of the two sinus beats preceding the PVC and the mean RR intervals of the two sinus beats following the PVC (see also Table 1). TS, turbulence slope, the maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC (see also Table 1). After the example of [21].

Methods

Design

A retrospective cohort study was conducted. QTV and HRT were calculated from 24-h Holter recordings of congenital heart disease patients with a systemic RV and from healthy controls. Correlation with clinical characteristics and outcomes was investigated. As this was a retrospective study, the need for informed consent was waived by the medical ethical committee of the Leiden University Medical Center.

Inclusion of patients and controls

In the electronic patient record system, 24-h Holter recordings of adult patients with a systemic RV were screened for suitability. The most recent suitable Holter, in which both QTV and HRT analysis could technically be performed, was selected. A control group was formed by consecutive patients referred for cardiac screening because of possible genetic cardiac abnormalities. As part of the screening protocol, 24-h Holter monitoring, echocardiography, genetic testing, and (bicycle) exercise test were conducted. Control subjects were eligible for inclusion if no genetic abnormalities and no abnormalities in the cardiac investigations were found. Protocols and used reference values for the exercise tests are in accordance with the ACC/AHA guidelines [14].

Exclusion criteria

If no interpretable Holter recordings were available, patients or controls were excluded. Holters with a non-sinus primary rhythm, Holter recordings lasting <18 h, or of insufficient quality were excluded. Patients or controls were excluded if they had clinically relevant diabetes (defined as the use of at least one antidiabetic drug), had rheumatoid arthritis, or were using antidepressant or antipsychotic medication, as these factors may interfere with cardiac autonomic function [15-17]. Additionally, controls were excluded in the case of relevant cardiac disease.

Holter processing

For the patient group, the most recent suitable Holter recording per patient was analyzed (*Table 1*). In the control group, also the most recent and usually the only Holter recording per subject was analyzed. Registrations were manually screened for correct labelling and onset of the QRS-complexes using a dedicated program [MARS, version 8 (GE Healthcare, Milwaukee, WI, USA). Episodes with predominant atrial or ventricular ectopy, atrial pacing, unclear atrial rhythm, inconsistent p-waves or PR intervals, junctional rhythm, or alternating grades of atrioventricular block were manually excluded as they would lead to distorted QTV and HRT calculation.

Table 1: QTV and HRT parameters

Abbreviation	Parameter	Calculation	Represents	Interpretation
VRa	Variability ratio of 5-minute averages	$\frac{SDQTa}{SDANN}$	Sympathetic activity	Higher values associated with adverse outcome
QTVi_a	QT interval variability index of 5-minute averages	$log\frac{QTVaN}{HRVaN}$	Sympathetic activity	Higher values associated with adverse outcome
TO (%)	Turbulence onset	$\frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})}$	Parasympathetic activity	Higher (less negative) values associated with adverse outcome
TS (%)	Turbulence slope	The maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC	Parasympathetic activity	Lower values associated with adverse outcome
HRT 0	Heart rate turbulence category 0	TO<0% and TS>2,5%	Parasympathetic activity	Normal
HRT 1	Heart rate turbulence category 1	TO>0% OR TS<2,5%	Parasympathetic activity	Moderately abnormal
HRT 2	Heart rate turbulence category 2	TO>0% AND TS<2,5%	Parasympathetic activity	Severely abnormal

HRVaN: normalised 5-min averaged heart rate variance; QTVaN: normalised 5-min averaged QT interval variance; RR_1 and RR_2: the two sinus beats following the premature ventricular complex; RR_{-1} and RR_{-2}: the two sinus beats preceding the premature ventricular complex; SDANN: standard deviation of 5-min averaged normal-to-normal/sinus intervals; SDQTa: standard deviation of 5-min averages of all QT intervals; TO: turbulence onset; TS: turbulence slope [9, 19, 20].

Calculation of QT variability

Within MARS, standard QT-analysis was performed, which yields graphs with QT-intervals over time. As MARS does not allow listing of all QT-intervals, dedicated software was designed (by co-author ACM) to extract average values of QT-intervals over 5-min intervals from these graphs. The following variables were recorded or calculated: mean QT interval, mean heart-rate corrected QT interval according to Bazett [18], the standard deviation of the 5-min averaged QT intervals (SDQTa), the 5-min averaged variability ratio (VRa), and the 5-min averaged QTV index (QTVi_a). The VRa was calculated by dividing SDQTa by SDANN (standard deviation of 5-min averaged normal-to-normal/sinus intervals), with the aim of correcting the QTV for variability in heart rate. This is a parameter with the same rationale as the VR coined by Jensen et al. [19], but presently calculated with 5-min averages while Jensen et al. used all QT-intervals and divided them by SDNN (standard deviation of all normal-to-normal intervals). The QTV index (QTVi) as coined by Berger et al. [20] was calculated by taking the logarithm of the ratio of normalized QT variance to heart rate variance, again using the 5-min averages of the QT-intervals and also 5-min averages of heart rate (QTVi_a). See Table 1 for QTV variables. For all QTV parameters, Holter lead 2 was used, as this lead is most similar to electrocardiogram lead II, the use of which is recommended in the position statement by the European Heart Rhythm Association to facilitate comparison between studies [9].

Calculation of heart rate turbulence

For the analysis of HRT, lists of interbeat intervals with appropriate labelling of normal beats, non-sinus supraventricular beats, and PVCs were exported from MARS and processed with dedicated software (written by co-author SM), which identified suitable PVCs according to the consensus statement by the International Society for Holter and Noninvasive Electrophysiology [21]. Most importantly, the PVC should be singular, should be preceded by at least two normal sinus beats, and should be followed by at least 15 normal sinus beats. HRT can reliably be calculated when at least five suitable PVCs have occurred during a recording. Subsequently, turbulence onset (TO) and turbulence slope (TS) were calculated. TO is the percentage of difference between the mean RR intervals of the two sinus beats preceding the PVC and the mean RR intervals of the two sinus beats following the PVC. TS is the maximum positive regression slope over any five consecutive RR intervals of the first 15 sinus beats after the PVC (*Fig. 1*).

Holter recordings were divided into HRT category 0, 1, or 2. Category 0 represents normal HRT and includes patients with TO < 0% and TS > 2,5%, or patients without enough PVCs for valid HRT calculation. Category 1 represents moderately abnormal HRT and includes patients with TO > 0% OR TS < 2,5%, and category 2 represents

severely abnormal HRT and includes patients with TO > 0% AND TS < 2,5%, representing moderately and severely abnormal HRT, respectively [21]. In the present study we made 1 exception: patients with 20 or more PVCs but with <5 PVCs suitable for HRT calculation were classified as 'undefined' instead of category 0. See *Table 1* for HRT variables.

Sick sinus syndrome may theoretically influence QTV and HRT calculation. However, because (episodes of the) Holters exhibiting signs of sinus node dysfunction were thus manually excluded, and because both QTV and HRT are calculated by averaging a multitude of values, the effect of sinus node dysfunction is minimized. Therefore, we did not specifically assess its influence on QTV and HRT in this study.

Clinical characteristics and endpoints

The event score was defined as the sum of all relevant clinical events per patient up until the time of the Holter. The following events were scored: supraventricular arrhythmias (SVT) for which treatment was initiated, or persistent and accepted supraventricular arrhythmias; (attempted) ablation of supraventricular arrhythmia; ventricular arrhythmias lasting >30 s or adequate implantable cardioverter-defibrillator (ICD) therapy; (attempted) ablation of ventricular arrhythmia; implantation of ICD (grouped under tachy-arrhythmia); implantation of pacemaker (categorized as brady-arrhythmia); hospital admission for cardiac decompensation; start or increase in dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs), diuretics, β-blockers, or other medication indicated due to heart failure (temporary increase in dose of e.g. diuretics, was included if the increase was for longer than 1 day) (grouped as heart failure); tricuspid valve repair or replacement (TVP/TVR). See also *Online Table 1*. As the relative impact of these events on QTV and HRT are unknown, each event was weighed equally. Other clinical data were collected dating from the same time or no more than 1 year apart (before or after) from the Holter recording and included age, length, weight, body surface area, New York Heart Association (NYHA) functional classification, results of bicycle exercise tests in terms of maximum achieved Watts and percentage of predicted number of Watts, and echocardiographic global systemic ventricular function. Offline measurement of global longitudinal strain of the systemic ventricle in the apical four-chamber view was performed [22]. Echocardiograms had been obtained with commercially available ultrasound systems and offline analysis was performed in EchoPac, GE Medical Systems (Little Chalfont, UK).

Statistical analysis

IBM SPSS statistics version 23 (Armonk, NY, USA) was used. Data were reported as mean ± SD or median-interquartile range as appropriate. The independent samples T-test, Mann-Whitney-U test, chi-square test, or Fisher's exact test were used for the comparison of clinical characteristics, QTV, and HRT between patients and controls, as appropriate. Spearman's rho correlation coefficients were calculated to assess correlations between QTV/HRT and clinical characteristics or events. Multivariate linear regression was used to assess the associations of QTV and HRT with the clinical event score. For all analyses, a p-value <0.05 was considered statistically significant.

Results

Patient selection and baseline characteristics

QTV and HRT were calculated for 40 patients (*Fig.* 2). QTV and HRT were calculated for 37 consecutive controls. The patient and control groups were comparable in terms of age and sex. The patient group used more medication, had a worse exercise capacity, and reduced echocardiographic function of the systemic ventricle compared with controls. Most patients were in NYHA class 1 or 2. The vast majority of controls was in NYHA class 1 (*Table* 2).

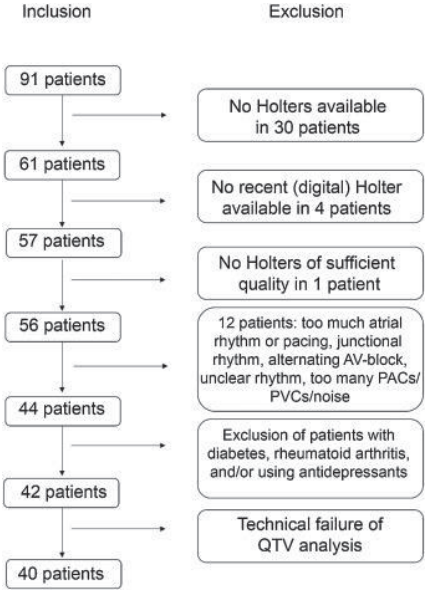

Figure 2. Flowchart for patient selection.
AV, atrioventricular; PAC, premature atrial complex; PVC, premature ventricular complex; QTV, QT interval variability.

Table 2. Baseline characteristics based on most recent Holter for QT interval variability

Characteristics	Patients N (%)	Mean±SD or median [IQR]	*Controls*	Mean±SD or median [IQR]	p-value
Total/females	40/16 (100%/40%)		37/21 (100%/57%)		0.141
Primary condition:					
TGA (Mustard)	10 (25%)		n.a.		
TGA (Senning)	18 (45%)		n.a.		
ccTGA	12 (30)		n.a.		
Age (years)		40±9		42 (±13)	0.451
NYHA class					
1	20 (50%)		35 (95%)		<0.001
2	16 (40%)		2 (5%)		
3	4 (10%)		0 (0%)		
BSA (m^2)		2.0±0.2		1.9 (±0.2)	0.098
Medication use:					
β-blocker	6 (15%)		0 (0%)		0.026*
ACEi or ARB	17 (43%)		1 (3%)		<0.001*
Diuretic	9 (23%)		1 (3%)		0.010*
Bm/AC	2 (5%)		5 (14%)		0.251
Digoxin	1 (3%)		0 (0%)		1.000
Amiodarone	1 (3%)		0 (0%)		1.000
Flecainide	2 (5%)		0 (0%)		0.494
Watts (ergometry)		160 [120-200]		200 [160-236]	0.007*
Validity (%)(ergometry)		93 [75-112]		123 [108-142]	<0.001*
Systemic ventricular GLS[1] (echocardiography)		-15.0±2.0		-20.2±2.7	<0.001*
Systemic ventricular function by eyeballing[2]					<0.001*
good (1)	2 (5%)		35 (97%)		
mildly reduced (2)	26 (70%)		1 (3%)		
moderately reduced (3)	9 (25%)		0 (0%)		
severely reduced (4)	0 (0%)		0 (0%)		
Number of previous thoracic surgeries					
0	8 (20%)		37 (100%)		<0.001*
1	16 (40%)				
2	12 (30%)				
3	4 (10%)				

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; Bm/Ac, betamimetic or anticholinergic drug; BSA, body surface area; ccTGA, congenitally corrected transposition of the great arteries; GLS, global longitudinal strain; IQR, interquartile range; NYHA, New York Heart Association classification of heart failure; SD, standard deviation; TGA (Mustard/Senning), after Mustard/Senning correction for transposition of the great arteries.

**significant p-value; 1: 3 patients and 1 control excluded: no (qualitatively sufficient) available images; 2: 2 patients and 1 control excluded: no (qualitatively sufficient) available images.*

QTV and HRT in patients and controls

QT intervals were significantly longer in patients. QTV was significantly increased in the patient group. HRT did not differ significantly between patients and controls (*Table 3*).

Of note, VRa was higher in women in the patient group (p = 0.041) and QTVi_a was higher in women in the control group (p = 0.034). There were no sex differences in QT intervals, QTc intervals, or HRT in either group (see *Online Table 2* for detailed information). There were no significant differences in QTV or HRT between patients after the atrial switch (Mustard or Senning) procedure for TGA and patients with ccTGA (see *Online Table 3* for detailed information).

Table 3. QT interval variability and HRT in patients and controls

		N	mean	±SD	*p*-value
Mean QT (ms)	Patients	40	425	±36	<0.001*
	Controls	37	394	±24	
Mean QTc (ms)	Patients	40	460	±28	<0.001*
	Controls	37	436	±17	
SDQTa	Patients	40	36	±11	0.032*
	Controls	37	31	±7	
VRa	Patients	40	0.30	±0.08	<0.001*
	Controls	37	0.22	±0.04	
QTVi_a	Patients	40	-0.51	±0.17	<0.001
	Controls	37	-0.74	±0.13	
TO[1] (%)	Patients	34	-2.5	±1.7	0.116
	Controls	14	-3.4	±2.3	
TS[1] (%)	Patients	34	8.6	±5.2	0.071
	Controls	14	12.4	±8.8	
			Count	%	
HRT category 0	Patients	40	36	90	
HRT category 1			2	5	
HRT category 2			2	5	
					0.611
HRT category 0	Controls	37	36	97	
HRT category 1			1	3	
HRT category 2			0	0	

**significant p-value; 1: 6 patients and 13 controls excluded because an insufficient number of suitable premature ventricular complexes was available for calculation of TO and TS; HRT, heart rate turbulence; 2: concerning the difference in HRT category between patients and controls; QTVi_a, QTV index of 5-minute averaged QT intervals; TO, turbulence onset; TS, turbulence slope; VRa, variability ratio of 5-minute averaged QT intervals.*

QTV, HRT, and clinical characteristics in patients with a systemic RV

Several types of medication correlated with increased QTV and/or more abnormal HRT, especially diuretics and flecainide. Decreased systemic RV function (less negative global longitudinal strain) correlated with increased QTV. Increased QTV and decreased HRT correlated with a higher event score (*Table 4*). Correlations between clinical events that occurred up until the time of the analyzed Holter recording (i.e. the components of the event score) are also shown in *Table 4*. Types of events were grouped in categories (see *Online Table 1* for detailed information). Increased QTV and decreased HRT correlated with a higher number of tachy-arrhythmia-related events (which were mainly SVTs). The correlations between tachy-arrhythmias (category within the event score) and QTV/HRT were similar to the correlations between solely SVTs (part of tachy-arrhythmias) and QTV/HRT (*Table 4* and *Online Table 1*). Decreased HRT correlated with heart failure (including hospitalization for decompensated heart failure and increases in heart failure medication) and TVP/TVR. The TVP/TVR procedures occurred 2 months, 2 months, and 6 years before the Holters of the respective patients. Of the other thoracic surgical procedures, none occurred more recently than 15 years before the Holter. Neither QTV nor HRT correlated with the number of previous thoracotomies (excluding the 3 TVP/TVR patients).

Table 4 Correlations between patient QTV/HRT, medication, and clinical characteristics

		VRa	QTVi_a	TO	TS	HRT category
β-blocker	Rho	0.24	0.23	0.09	-0.09	0.08
	P	0.131	0.152	0.617	0.617	0.617
ACEi/ARB	Rho	0.31	**0.33**	0.15	-0.12	**0.39**
	P	0.052	**0.040***	0.394	0.507	**0.014***
Digoxin	Rho	0.21	0.16	0.26	-0.29	**0.51**
	P	0.213	0.325	0.142	0.093	**0.001***
Amiodarone	Rho	0.13	0.19	-	-	-0.05
	P	0.418	0.247			0.744
Flecainide	Rho	**0.33**	0.29	0.31	-0.26	**0.33**
	P	**0.039***	0.071	0.079	0.146	**0.041***
Diuretic	Rho	0.27	**0.35**	**0.39**	**-0.53**	**0.41**
	P	0.089	**0.029***	**0.022***	**0.001***	**0.009***
Bm/Ac	Rho	-0.06	0.14	0.05	0.00	-0.08
	P	0.715	0.392	0.775	1.000	0.640
Thoracic surgeries[1]	Rho	-0.14	0.03	0.07	-0.14	0.09
	P	0.415	0.868	0.712	0.453	0.583
Watts	Rho	-0.29	-0.24	-0.39	0.39	-0.38
	P	0.178	0.269	0.087	0.093	0.072
Validity	Rho	-0.12	-0.33	-0.39	0.25	-0.35
	P	0.594	0.129	0.087	0.282	0.098
RV-GLS	Rho	0.25	**0.33**	0.35	-0.26	0.16
	P	0.134	**0.048***	0.055	0.163	0.343
Event score	Rho	0.26	**0.43**	**0.38**	**-0.48**	**0.40**
	P	0.099	**0.006***	**0.027***	**0.004***	**0.011***
Components of event score						
Tachy-arrhythmia	Rho	**0.43**	**0.45**	0.32	**-0.46**	**0.36**
	P	**0.005***	**0.004***	0.064	**0.007***	**0.023***
Brady-arrhythmia	Rho	0.01	0.22	0.18	-0.13	-0.11
	P	0.930	0.180	0.317	0.463	0.495
Heart failure	Rho	0.21	0.31	0.30	-0.30	**0.47**
	P	0.188	0.052	0.089	0.090	**0.002***
TVP/TVR	Rho	0.11	0.10	**0.46**	**-0.42**	**0.54**
	P	0.495	0.528	**0.006***	**0.014***	**<0.001***

**significant p-value; 1: excluding 3 patients who underwent tricuspid valve replacement or repair. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; Bm/Ac, betamimetic or anticholinergic drug; GLS, global longitudinal strain; HRT, heart rate turbulence; QTV, QT interval variability; QTVi_a, QTV index of 5-minute averaged QT intervals; RV, right ventricular; TO, turbulence onset; TS, turbulence slope; TVP/TVR, tricuspid valve repair or replacement; VRa, variability ratio of 5-minute averaged QT intervals.*

When patients without PVCs were excluded (N = 6), patients with a higher number of PVCs had a significantly higher HRT category (p = 0.026) (*Fig. 3*).

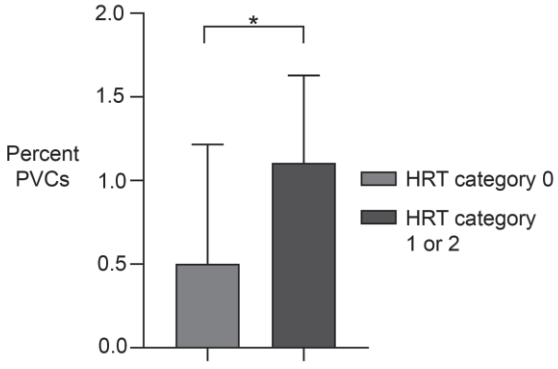

Figure 3. HRT category and percentage of PVCs in the patient group.

HRT, heart rate turbulence; PVC, premature ventricular complex. Patients in HRT category 1 or 2 (reduced HRT) have more PVCs than patients in HRT category 0 (normal HRT).

Factors associated with the event score

To investigate the association between QTV and HRT and clinical outcome, linear regression for the event score was performed. In the univariate analysis, higher QTV and worse HRT are associated with a higher event score. In the multivariate analysis, TS remains independently associated with the event score, in addition to exercise capacity and the use of ACE inhibitors/ARBs (*Table 5*).

Correlation between QTV and HRT

VRa and QTVi_a were not correlated with either TO or TS. TO and TS were strongly correlated, and VRa and QTVi_a were strongly correlated. Thus, QTV variables correlated with each other and HRT parameters correlate with each other, but QTV and HRT do not correlate with each other. This indicates that QTV and HRT reflect two different pathways (data in *Online Table 4*).

Table 5 Linear regression for the event score

Linear regression	Estimate univariate (95% CI)		p-value univariate	Estimate multivariate (95% CI)		*p*-value multivariate
Variable						
Age	0.11	(-0.02 – 0.24)	0.096			
Gender	0.98	(-1.57 – 3.53)	0.441			
Watts	-0.06	(-0.09 - -0.03)	**0.001***			NS
RV GLS	1.10	(0.52 – 1.68)	**<0.001***	0.99	(0.35 – 1.63)	0.004*
BSA	4.61	(-2.31 – 11.52)	0.185			
VRa	18.72	(4.12 – 33.31)	**0.013***			NS
QTVi_a	9.88	(3.16 – 16.61)	**0.005***			NS
TO	1.00	(0.21 – 1.79)	**0.015***			NS
TS	-0.36	(-0.61 - -0.12)	**0.005***	-0.24	(-0.46 - -0.03)	<0.001*
HRT category	3.29	(0.88 – 5.69)	**0.009***			NS
Use of:						
β-blocker	4.10	(0.84 – 7.35)	**0.015***			NS
ACEi/ARB	3.94	(1.75 – 6.14)	**0.001***	3.34	(1.22 – 5.47)	<0.001*
Digoxin	0.15	(-7.91 – 8.21)	0.969			
Amiodarone	2.21	(-5.82 – 10.23)	0.581			
Flecainide	1.74	(-4.01 – 7.48)	0.544			
Diuretic	6.07	(3.81 – 8.33)	**<0.001***			NS

**significant p-value. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; BSA, body surface area; CI, confidence interval; HRT, heart rate turbulence; NS, not significant; QTVi_a, QT interval variability index of 5-min averaged QT intervals; RV GLS, right ventricular global longitudinal strain; TO, turbulence onset; TS, turbulence slope; VRa, variability ratio of 5-min averaged QT intervals.*

Discussion

Key findings of this study are: in patients with a systemic RV, both QTV and HRT were associated with clinical events (TS independently), including tachy-arrhythmias (mainly SVTs). QTV was increased in patients compared with controls.

Both QTV and HRT appear related to deteriorating clinical condition in patients with a systemic RV. TS was independently associated with clinical (mainly arrhythmia- and heart failure related) events. Increased QTV correlated with reduced systemic RV function. The use of flecainide, diuretics, and ACE inhibitors/ARBs correlated with increased QTV and decreased HRT. Digoxin correlated with decreased HRT. These results may indicate that worse clinical status, translating into medication requirement, is associated with abnormal QTV and HRT. Medication may also influence autonomic function directly. While flecainide may enhance sympathetic function [23], ACE inhibition and diuretic treatment tend to restore autonomic function [24, 25], and digoxin increases parasympathetic activity [26]. The observations are in line with previous research: in children with atrial septal defect, QTV was increased and correlated with the left-to-right shunt ratio [27]. In adults with tetralogy of Fallot, abnormal HRT was related to both worse left ventricular and right ventricular function and worse exercise capacity [5].

In patients with a systemic RV, QTV and HRT correlated with SVTs. In this population, SVTs are an important predictor of mortality [28, 29]. Several mechanisms might explain this observation. Systemic RV failure leads to increased sympathetic output, which is reflected in QTV and HRT and predisposes to atrial tachycardias or fibrillation [30]. SVTs by themselves can further decrease systemic RV function, resulting in progressive autonomic adaptation, also causing changes in QTV and HRT. In addition, intrinsic atrial abnormalities, which predispose to SVTs, are common in patients with a systemic RV due to atrial scar tissue or congenital conduction abnormalities [31]. These can cause abnormal QTV as atrial refractoriness is a component of the QT interval [32]. Previous research in patients with left-sided cardiac disease also show associations between QTV/HRT and SVTs [2, 8].

The increased QTV may indicate repolarization instability and possibly a higher risk for ventricular arrhythmias [9]. The mechanism is probably spontaneous variable diastolic calcium release caused by sympathetic stimulation following reduced systemic RV function [33]. This leads to variable action potential duration [34] and therefore increased QTV [9]. However, autonomic innervation of the systemic RV may also be inherently different as a result of abnormal cardiac development. This might differ

between individual patients, as the group is heterogeneous. If so, this might partly explain why not all ventricular arrhythmias occur in patients with reduced systemic RV function [35], which makes it difficult to estimate which patients benefit from ICD implantation. In a large cohort of patients with structural heart disease and an ICD, increased QTV predicted ventricular arrhythmias [3].

In the studied population, surgical denervation may have occurred. This could theoretically have influenced the observed results. However, we showed no differences in QTV and HRT between patients with TGA after atrial switch and ccTGA patients. The number of previous (early) thoracotomies was not correlated with either QTV or HRT. Indeed in previous studies, recovery of autonomic function was usually seen in a matter of months after thoracic surgery, indicating functional re-innervation [36, 37]. Also, in contrast to the currently used arterial switch procedure, in the atrial switch procedure, the great arteries, and therefore the nerves alongside them, are not transected [38].

In contrast, previous TVP/TVR did correlate with decreased HRT. As these procedures were more recent, surgical denervation may have played a role. A study in patients without congenital heart disease, after undergoing mitral valve replacement, also showed depressed autonomic function. However, follow-up time was relatively short and therefore did not allow assessment of long-term recovery [39]. Next to surgical denervation, autonomic adaptation due to hemodynamic factors may also play a role. Systemic RV patients after TVP/TVR have experienced a period of volume overload due to tricuspid valve regurgitation, followed by relative pressure overload after surgery. This may induce autonomic adaptation similar to heart failure.

In both patients and controls, QTV (and not the QT and QTc intervals) was increased in women, suggesting a potentially higher arrhythmic risk. Previous literature is conflicting. Some studies report no gender differences [40], while others report higher QTV in women [41].

HRT was not significantly different in patients and controls. There was a trend toward lower TS in the patient group. The lack of a significance is likely due to the limited sample size, as previous research indicates a clear difference in HRT between (non-congenital) heart failure patients and controls [6].

To our knowledge, this is the first study to describe QTV and HRT in a cohort of patients with a systemic RV. They may be suitable monitoring tools for heart failure and arrhythmia risk in these patients and have potential use in ICD-related decision making.

Assessment of both QTV and HRT is likely more valuable than either alone, as they were not correlated and thus likely reflect different pathways. This study was limited by the required sinus rhythm for analysis of both QTV and HRT: this may have caused selection bias. However, QTV and HRT may be especially useful early in disease progression, when most patients are in sinus rhythm and do not have clear signs and symptoms of heart failure yet. Analysis of the association between QTV/HRT and ventricular arrhythmias was limited by the small number of events. QTV analysis was performed on 5-min averaged values instead of from consecutive QT intervals. This limits comparability with other studies. TO and TS could not be calculated in all subjects because of a lack of suitable PVCs. In the future, this could be overcome in patients with intracardiac leads or during a percutaneous cardiac procedure, with induced HRT: calculation of HRT after a 'PVC' simulated by intracardiac pacing [42]. The likelihood of finding enough suitable PVCs can also be increased by using 48-h Holter monitoring or continuous monitoring through implantable or wearable devices.

In conclusion, QTV and HRT are associated with clinical factors and events in congenital heart disease patients with a systemic RV. Prospective research is needed to confirm their prognostic value. Monitoring of QTV and HRT might be useful in the assessment of arrhythmia risk and clinical deterioration in this patient group.

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Part II: Clinical applications

Chapter 5

Validation and Feasibility of Echocardiographic Assessment of Systemic Right Ventricular Function: Serial Correlation With MRI

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Abstract

Background

Inherent to its geometry, echocardiographic imaging of the systemic right ventricle (RV) is challenging. Therefore, echocardiographic assessment of systemic RV function may not always be feasible and/or reproducible in daily practice. Here, we aim to validate the usefulness of a comprehensive range of 32 echocardiographic measurements of systemic RV function in a longitudinal cohort by serial assessment of their correlations with cardiac magnetic resonance (CMR)-derived systemic RV ejection fraction (RVEF).

Methods

A single-center, retrospective cohort study was performed. Adult patients with a systemic RV who underwent a combination of both CMR and echocardiography at two different points in time were included. Off-line analysis of echocardiographic images was blinded to off-line CMR analysis and vice versa. In half of the echocardiograms, measurements were repeated by a second observer blinded to the results of the first. Correlations between echocardiographic and CMR measures were assessed with Pearson's correlation coefficient and interobserver agreement was quantified with intraclass correlation coefficients (ICC).

Results

Fourteen patients were included, of which 4 had congenitally corrected transposition of the great arteries (ccTGA) and 10 patients had TGA late after an atrial switch operation. Eight patients (57%) were female. There was a mean of 8 years between the first and second imaging assessment. Only global systemic RV function, fractional area change (FAC), and global longitudinal strain (GLS) were consistently, i.e., at both time points, correlated with CMR-RVEF (global RV function: $r = -0.77/r = -0.63$; FAC: $r = 0.79/r = 0.67$; GLS: $r = -0.73/r = -0.70$, all p-values < 0.05). The ICC of GLS (0.82 at $t = 1$, $p = 0.006$, 0.77 at $t = 2$, $p = 0.024$) was higher than the ICC of FAC (0.35 at $t = 1$, $p = 0.196$, 0.70 at $t = 2$, $p = 0.051$) at both time points.

Conclusion

GLS appears to be the most robust echocardiographic measurement of systemic RV function with good correlation with CMR-RVEF and reproducibility.

Introduction

In congenital heart disease with a systemic right ventricle (RV), the RV supports systemic circulation. This includes transposition of the great arteries (TGA) after atrial switch operation and congenitally corrected TGA (ccTGA) (*Figure 1*). The systemic RV is morphologically and functionally different from the left ventricle (LV) and is more suitable to process volume than pressure. Systemic RV failure is a well-known, long-term complication as are tricuspid valve regurgitation, conduction abnormalities, and arrhythmias (1, 2). Progression from subclinical to clinical systemic RV dysfunction can be sudden and unexpected, hampering identification of the ideal window of intervention. Early and reliable detection of reduced systemic RV function is essential but challenging for several reasons. The shape of the systemic RV limits the possibilities for calculations based on spatial assumptions, such as ejection fraction (3), and pronounced trabeculations impair the measurement of the volume of the systemic RV. Cardiac magnetic resonance (CMR) imaging is regarded as the gold standard for volumetric and functional assessment of systemic RV (4, 5) although it is often not feasible because patients may have pacemakers or implantable cardioverter defibrillators with epicardial or abandoned leads. Thus, transthoracic echocardiography (TTE) is still the main tool for the assessment of systemic RV function in clinical practice (3). Previous studies evaluated echocardiographic indices of systemic RV function, such as global longitudinal strain (GLS), fractional area change (FAC), isovolumic acceleration (IVA), the myocardial performance index (MPI), and tricuspid annular plane systolic excursion (TAPSE), which may all have value in the evaluation of systemic RV function (6–15).

There is a gap between the research setting and daily clinical practice: systemic RV geometry in combination with previous thoracotomies makes specific echocardiographic views difficult to obtain. Reported correlations between echocardiographic variables and CMR-derived RVEF differ (3), and interobserver variability may influence the reliability of individual measurements (11, 16, 17). No studies have evaluated the consistency of the correlation between both imaging techniques over time.

This study aims to distill echocardiographic variables that are feasible to obtain in daily clinical practice, are consistently correlated with CMR-derived RVEF, and can be measured reliably.

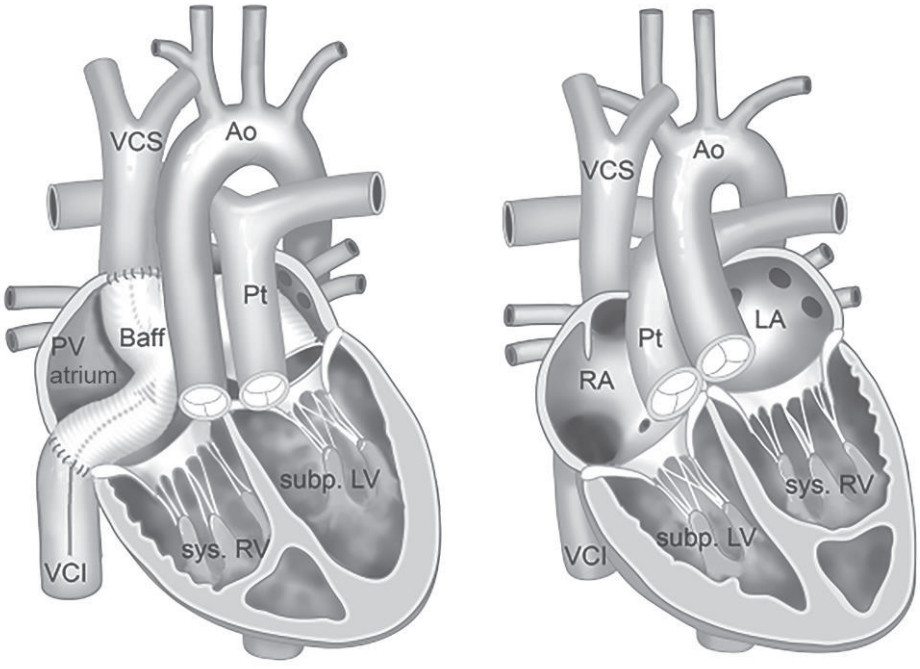

Figure 1

(A) Transposition of the great arteries after Mustard or Senning repair. (B) Congenitally corrected transposition of the great arteries. Ao, aorta; Baff, systemic venous baffle; LA, (morphologically) left atrium; Pt, pulmonary trunk; PV atrium, pulmonary venous atrium; RA, (morphologically) right atrium; Subp. LV, subpulmonary LV; Sys. RV, systemic RV; VCI, inferior vena cava; VCS, superior vena cava.

Methods

We aimed to validate the usefulness of a comprehensive range of echocardiographic variables of systemic RV function in a single-center cohort. Echocardiographic variables were compared with CMR-RVEF at two different points in time. All reported echocardiographic variables of systemic RV function were included. When applicable, different methods of evaluating a single variable were compared. Interobserver agreement and feasibility of the variables were assessed.

Study Design and Patient Selection

A retrospective cohort study was conducted. Adult patients with a systemic RV in a biventricular circulation (TGA after Mustard or Senning procedure or ccTGA) from the outpatient congenital cardiology clinic of the Leiden University Medical Center were screened for availability of a combination of both CMR and TTE images at two different

points in time at least 5 years apart. The CMR and TTE images at the same points in time should be no more than 1 year apart. All consecutive patients meeting these criteria were included. Complex (cc)TGA was defined as (cc)TGA with important additional malformations present at birth, including ventricular septal defects, left ventricular outflow tract (LVOT) obstruction, and aortic arch malformations. The Leiden University Medical Center's medical research ethics committee waived the need for informed consent. The protocol is in accordance with the 2013 Declaration of Helsinki.

Selection of Echocardiographic Variables

To identify a comprehensive range of echocardiographic variables of systemic RV function, a PubMed search was conducted with the following key terms: "systemic right ventricle," "(congenitally corrected) transposition of the great arteries," "echocardiography," "atrial switch," "Mustard," "Senning." From the articles found, studies in which echocardiography was conducted in cohorts of patients with a systemic RV (TGA after atrial switch procedure, ccTGA, or both) were screened for echocardiographic variables reflecting systemic RV function. Both studies in which echocardiographic variables were compared with CMR-RVEF and studies assessing associations between echocardiographic variables and clinical variables (such as exercise capacity) or clinical events/outcomes were screened. From these studies, all variables that could be reasonably measured in our cohort were added to the protocol.

Echocardiography

Clinically indicated echocardiograms performed with commercially available ultrasound systems were analyzed off-line in EchoPac, GE Medical Systems. Length, weight, and heart rate at the time of imaging were noted. Measurements were performed off-line by one researcher (TZ) who received training from three experienced congenital imaging cardiologists: PK (European Association of Cardiovascular Imaging [EACVI] certified for >10 years), DH (EACVI member), and EH (head of the imaging lab, supervisor of EACVI candidates). To assess interobserver agreement, measurements were repeated by PK in half of the echocardiograms, blinded to the measurements of TZ. Both observers were blinded to the MRI measurements. *Table 1* describes the variables that were measured or calculated. If several methods to calculate the same variable were available, all were applied to allow comparison (e.g., MPI). In total, 32 variables of systemic RV function were assessed. For completeness, atrial dimensions and subpulmonary LV function variables were additionally assessed.

Table 1: Echocardiographic variables studied

Variable and view	Specification	Unit	Reference values
Dimensions			
LA length[a]	Left atrial end-systolic length	mm	
LA volume index (LAVI)[a]	Left atrial end-systolic volume (Simpson's biplane method) indexed by body size	mL/m²	
RA length[a]	Right atrial end-systolic length	mm	
RV apex-base length	RV end-diastolic length	mm	84 mm (11)
Mid-RV diameter	RV end-diastolic diameter at half of the apex-base length	mm	
RV base diameter	Maximal RV end-diastolic diameter in basal 1/3 of the ventricle	mm	49 mm (11); 47 mm (12); 45.6 mm (18)
RV free wall thickness	End-diastolic thickness in PLAX	mm	10 mm (18)
Systemic RV function			
RV global function	Visual assessment of systemic right ventricular function	Normal, mildly abnormal, moderately abnormal, severely abnormal	62% moderately or severely abnormal (11)
RV FAC	Fractional area change: (RV end-diastolic area-RV end-systolic area)/RV end-diastolic area*100%	%	31.7% (19); 24% (11); 32% (12); 23% (20); 22.9% (18); 38.7% (9); 44%• (14); 38% (15)
RV GLS	Maximum global longitudinal strain in AP4CH	%	−13.3% (21); −14.2% (11); −12% (20); −13.5% (16); −12.5% (18); −18.7%• (14); −14.6% (15); −15.5% (12)
RV SR S	Maximum global systolic strain rate	%/s	−0.61%/s (15); −0.59 (18)
RV SR E	Maximum global strain rate during early diastole	%/s	0.68 (18)
RV SR A	Maximum global strain rate during late diastole	%/s	0.32 (18)
RV septal strain	Maximum mid-septal longitudinal strain in AP4CH	%	−12.2% (11); −12.1 (15)
RV septal SR S	Maximum mid-septal systolic strain rate	%/s	
RV septal SR E	Maximum mid-septal strain rate during early diastole	%/s	
RV septal SR A	Maximum mid-septal strain rate during late diastole	%/s	
RV free wall strain	Maximum mid-lateral longitudinal strain in AP4CH	%	−14.7% (11); −15.0 (15)
RV free wall SR S	Maximum mid-lateral systolic strain rate	%/s	−1.06%/s (11)
RV free wall SR E	Maximum mid-lateral strain rate during early diastole	%/s	
RV free wall SR A	Maximum mid-lateral strain rate during late diastole	%/s	
IVA PW-TDI AP4CH	Isovolumic acceleration: V_{max}/time to V_{max} during isovolumetric acceleration	m/s²	

IVA TDI AP4CH	Isovolumic acceleration: V_{max}/time to V_{max} during isovolumetric acceleration	m/s^2	0.9 m/s^2 (15); 1.33 (18)
MPI PW-TDI AP4CH	Myocardial performance index (Isovolumetric contraction time + isovolumetric relaxation time)/ejection time	–	
MPI TDI AP4CH	Myocardial performance index (Isovolumetric contraction time + isovolumetric relaxation time)/ejection time	–	0.41 (15); 0.53 (19)
MPI TV inflow/RV outflow	Myocardial performance index (Isovolumetric contraction time + isovolumetric relaxation time)/ejection time	–	0.57 (14); 0.47 (9); 0.63 (18)
MPI CW-TR/RV outflow	Myocardial performance index (Isovolumetric contraction time + isovolumetric relaxation time)/ejection time	–	
Tricuspid valve lateral velocity	Velocity measured with PW-TDI	cm/s	7.2 (8); 9 (12); 8 (15); 9.1 (14); 9.7 (9); 5.1 (18); 8 (16); 8.4 (11); 5.2 (19)
Tricuspid valve septal velocity	Velocity measured with PW-TDI		
TAPSE	Tricuspid annular plane systolic excursion	mm	12 mm (11); 12 mm (20); 13 mm (16); 9.8 mm (18); 14.3 mm (9); 16.4 mm • (14) 12.5 mm (15); 14 mm (12); 13 mm (8)
MAPSE septal	Mitral annular plane systolic excursion (septal aspect)		
Tricuspid valve dP/dt	Continuous wave Doppler tricuspid regurgitation: time between 1 and 3 m/s (=time necessary for RV pressure to increase 32 mmHg)	mmHg/s	1,625 (12); 868 (15); 1,167 (9); 1,024 (16); 833 (11);
Tricuspid valve regurgitation	Based on integration of a.o. jet density/contour, vena contracta width, and proximal isovelocity surface area-radius [see (22)]	Mild, moderate, severe	> mild: 40% (11); 63% (20); 33% (16)
Dyssynchrony			
Intraventricular delay (strain)	Time to peak strain RV free wall–time to peak strain RV septal wall	ms	48 ms (19)
Interventricular delay (strain)	Time to peak strain RV free wall—time to peak strain LV free wall	ms	63 ms (19)
Interventricular delay (output)	Time between Q wave and start output RVOT in CW Doppler—Time between Q wave and start output LVOT in CW Doppler	ms	50 ms (23)
Diastolic function systemic RV			
Tricuspid valve E/A ratio		–	1.7 (8)
Tricuspid valve E/e' ratio		–	7.6 (8)

Left ventricular dimensions and function			
Left ventricular end diastolic diameter	Measured in PLAX and AP4CH	mm	34 (14); 32 (19)
LV GLS	Maximum global longitudinal strain in AP4CH		−18.6% (21)
MAPSE	Mitral annular plane systolic excursion	mm	21.8 mm• (14); 19 mm (8)

[a]*only for patients with congenitally corrected transposition of the great arteries; AP4CH, apical four-chamber view; CW doppler, continuous wave doppler; FAC, fractional area change; GLS, global longitudinal strain; IVA, isovolumic acceleration; LA, left atrial; LV, left ventricle; LVOT, left ventricular outflow tract; MAPSE, mitral annular plane systolic excursion; MPI, myocardial performance index; PLAX, parasternal long-axis view; PW-TDI, pulsed-wave tissue doppler imaging; RA, right atrial; RV, right ventricle; RVOT, right ventricular outflow tract SR A, maximal late diastolic strain rate; SR E, maximal early diastolic strain rate; SR S, maximal systolic strain rate; TAPSE, tricuspid annular plane systolic excursion.*

(21): N = 129, Mustard/Senning/ccTGA, 31% NYHA>1. Mean RVEF 52%. (11): N = 42, Mustard/ccTGA, median NT-pro-BNP 27.4 pmol/L (232 ng/L) (20): N = 105, Mustard/Senning/ccTGA, 29% NYHA>1. Mean RVEF 42%, mean percent predicted peak VO_2 69%. (16): N = 35, Mustard/Senning. Twelve percent NYHA>1. Mean RVEF 44%. (18): N = 64, Mustard/Senning. Optimal cutoff for prediction of events (incident heart failure or ventricular tachycardia): GLS−10% (9): N = 37, Mustard/Senning. Twenty-two percent NYHA>1. Optimal cutoff for CMR-RVEF 50%: FAC 33%. (14): N = 33, ccTGA, 36% NYHA>1. Optimal cutoff for CMR-RVEF 45%: GLS−16.3%. •: values given for the part of the group with CMR-derived RVEF≥45%; (15): N = 47, Mustard/Senning, 13% NYHA>1. Median percent predicted peak VO_2 value 64.5%. Mean RVEF 47%. (12): N = 48, Mustard/Senning, mean RVEF: 48%. Optimal cut-off for RVEF 45%: FAC 29.5% and GLS−14.2%. (8): N = 46, Mustard/Senning/ccTGA, 24% NYHA>1. Median NT-pro-BNP 475 ng/L (23): N = 8, Mustard/Senning/ccTGA/DORV, undergoing CRT. Values given measured after CRT. (19): N = 28, Mustard/Senning, mean FAC = 31.7.

Global systemic RV function was visually assessed from the apical four-chamber view and parasternal long and short axis views. Systemic RV free wall thickness was measured in end-diastole in the parasternal long axis view. Systemic RV dimensions and areas and subpulmonary LV dimensions were measured in the apical four-chamber view in all patients. Trabeculations were included in the cavum. FAC was calculated as the percentage of change between the end-diastolic and end-systolic areas. Speckle tracking GLS and strain rate (SR) were determined in the apical four-chamber view by the software package in EchoPac after manual determination of the endocardial border (24). The placement of the automatically allocated markers was adjusted manually after visual inspection during movement to include the entire myocardium, including the free wall, apex, and septum. GLS was determined for both the systemic RV and subpulmonary LV. For the systemic RV, longitudinal strain and SR were also calculated separately for the mid-free wall and mid-septal regions. TAPSE and mitral annular plane systolic excursion (MAPSE) were determined in M-mode by placing the cursor in the lateral aspect of, respectively, the tricuspid and mitral valves. The effective regurgitant volume of the tricuspid valve was determined with the proximal isovelocity surface area method in the color doppler and continuous wave doppler images of the tricuspid valve (25). Early and late diastolic velocities were measured from the pulsed wave

doppler image of the tricuspid valve inflow. The rate of pressure build-up in the systemic RV (dP/dt) was calculated from the continuous wave image of tricuspid regurgitation in the interval for the regurgitation velocity to increase from 1 to 3 m/s. Tricuspid valve regurgitation itself was assessed semiquantitatively based on integration of several variables in accordance with the ESC recommendations as described elsewhere (22). The MPI was calculated as (isovolumic contraction time + isovolumic relaxation time)/ejection time. In patients with reduced ventricular function, the isovolumic contraction and relaxation times are longer and the ejection time shorter. Thus, a higher MPI reflects reduced ventricular function (26). MPI was calculated in four ways (*Supplementary Figure 1*): first, from the pulsed wave tissue doppler image of the tricuspid valve in the apical four-chamber view and, second, from manual analysis of the tissue doppler image. Third, it was calculated from the continuous or pulsed wave doppler image of the tricuspid valve inflow and the continuous or pulsed wave doppler image of the RV outflow tract. Last, it was calculated from the continuous wave signal of tricuspid valve regurgitation and the continuous or pulsed wave doppler image of the RV outflow tract. The first two methods only require one image, which limits variation because of heart rate but only uses the motion of the lateral aspect of the tricuspid valve and, therefore, may have the disadvantage of reflecting regional rather than global ventricular performance. The third and fourth methods may reflect ventricular performance more globally but have the disadvantage that measurements have to be performed in separate images, allowing differences in heart rate to introduce variation (27).

The isovolumic acceleration was calculated as the slope of velocity increase of the lateral aspect of the tricuspid valve during isovolumic contraction (28). It was calculated from the pulsed wave tissue doppler image of the lateral tricuspid valve in the apical four-chamber view and from the tissue doppler image in which the cursor was manually placed at the lateral aspect of the tricuspid valve.

Systolic and early and late diastolic velocities of the lateral aspect of the tricuspid valve and systolic velocity of the septal aspect of the tricuspid valve were measured in the pulsed wave tissue doppler and the tissue doppler apical four-chamber images.

Intraventricular dyssynchrony was calculated as the difference between the time to peak strain in speckle tracking analysis between the systemic RV mid-lateral and mid-septal wall (16, 19, 29). Interventricular dyssynchrony was calculated in two ways: as the difference between time to peak strain between the systemic RV mid-free wall and the subpulmonary LV mid-free wall and as the difference between onset of Q-start ejection between the RVOT and LVOT (30).

Cardiac Magnetic Resonance Imaging

MRI studies were performed with a 1.5-T whole-body MRI scanner (Philips Medical Systems, Best, the Netherlands). The routine clinical protocol included electrocardiographically gated breath-hold, steady-state, free precession imaging in transverse orientation. Length, weight, and heart rate at the time of imaging were noted. To assess cardiac dimensions and systolic function, end-diastolic and end-systolic endocardial contours were manually drawn with software (MASS; Medis Medical Imaging Systems, Leiden, the Netherlands) by an experienced cardiothoracic radiologist (RW) who was blinded to the echocardiographic measurements. Trabeculations were included in the cavity. Systemic RV dimensions and free wall thickness were measured in end-diastole in the four-chamber view. Stroke volume was calculated by subtracting the end-systolic from the end-diastolic volume. Systemic right ventricular ejection fraction (RVEF) was calculated as the percentage of volume change between the end-diastolic and end-systolic volumes. Cardiac output was calculated by multiplying the stroke volume by heart rate.

Statistical Analysis

For all analyses, IBM SPSS statistics 25 was used. Data are presented as mean ± standard deviation (SD) (or median and interquartile range [IQR] as appropriate) or frequencies and percentages. Changes between variables over time were tested with Student's T-test. Correlations between echocardiographic and CMR imaging variables were tested with Pearson's or Spearman's correlation analysis as appropriate. Interobserver agreement was visually assessed by calculation of the mean difference between observed values and constructing the limits of agreement (±1.96 SD of the difference, thus including 95% of measurements) according to Bland and Altman (31). Interobserver agreement was statistically assessed with calculation of intraclass correlation coefficients (ICC). Agreement between systemic RV dimensions as measured on the echocardiograms and the CMR images was also assessed with calculation of the ICC. All correlations and ICCs were calculated separately for the two points in time. P-values of < 0.05 were considered statistically significant.

Results

Patient Characteristics

Fourteen patients were included. The majority of patients underwent a Mustard or Senning procedure for TGA. Heart rate and body surface area were not significantly different between the first and the second time point. The QRS duration increased between the first and second time point; however, few patients had a QRS duration > 130 ms (1 at T = 1 and 2 at T = 2). The overall New York Heart Association (NYHA) class worsened between the first and second time points (*Table 2*).

Cardiac Function at T = 1 and T = 2

Overall, there were few significant changes in imaging variables between the first and second time points; only the echocardiographic RV apex-base diameter increased significantly (*Table 2*) (the CMR-derived apex-base diameter did not). To provide context for the values and aid in the interpretation, *Table 1* shows reference values for the variables given as published in 12 previous, frequently cited imaging studies in patients with systemic RV (*Table 1*).

Correlations Between Echocardiographic and CMR Variables

Only three echocardiographic variables of systemic RV function were consistently correlated with CMR-RVEF: visually assessed global systemic RV function (T = 1: $r = -0.77$ and $p = 0.002$; T = 2: $r = -0.63$ and $p = 0.024$), FAC (T = 1: $r = 0.79$ and $p = 0.001$; T = 2: $r = 0.67$ and $p = 0.018$), and GLS (T = 1: $r = -0.73$ and $p = 0.005$; T = 2: $r = -0.70$ and $p = 0.011$) (*Figure 2*). The late global diastolic SR of the systemic RV (SR A) was consistently significantly correlated with CMR-derived cardiac output. Septal SR A was consistently significantly correlated with LV SV (*Figure 3*). All other echocardiographic variables were not (consistently) significantly correlated with CMR variables (*Supplementary Tables 1–8*). As the variables describing atrial dimensions (*Table 1*) were less clinically relevant in the patients who underwent atrial switch (the majority) and, thus, had surgically altered atria, these variables were not analyzed further.

Table 2: Patient characteristics and imaging values at T=1 and T=2

Clinical characteristics	T=1 Mean±SD, median [IQR], or N(%)	T=2 Mean±SD, median [IQR], or N(%)	p-value
Female	8 (57%)		
ccTGA	4 (29%)		
Mustard/Senning	10 (71%)		
Complex (cc)TGA	9 (64%)		
VSD[1]	0 (0%)	0 (0%)	
LVOT stenosis[1]	4 (29%)	4 (29%)	
Prior TVR/TVP	0 (0%)	0 (0%)	
Age	35±7	43±7	
QRS duration (ms)	106 [92-116]	112 [108-119]	**0.038***
Heart rate (bpm)	70±17	69±15	0.342
Rhythm			1,000
Sinus rhythm	13 (93%)	12 (86%)	
Atrial rhythm	1 (7%)	2 (14%)	
BSA (m^2)	1.9 [1.8-2.0]	1.9 [1.8-2.0]	0.638
NYHA class			**0.025***
O I	7 (50)	2 (14)	
O II	6 (43)	11 (79)	
O III	1 (7)	1 (7)	
Echocardiographic variables			
RV apex base diameter (mm)	77±9	80±9	**0.011***
RV mid diameter (mm)	43±9	45±7	0.230
RV basal diameter (mm)	50±6	52±5	0.749
RV free wall thickness (mm)	8±2	9±4	0.432
RV FAC (%)	27±7	24±5	0.071
RV global function moderately or severely reduced (N, %)	3 (21%)	4 (29%)	0.317
RV GLS (%)	-14.5±3.0	-15.0±2.7	0.508
TAPSE (mm)	12±3	14±2	0.304
Tricuspid regurgitation > mild (N, %)	5 (36%)	4 (29%)	0.813
LV GLS (%)	-20.9±3.7	-19.4±2.5	0.283
MAPSE (mm)	19±3	20±4	0.673
CMR variables			
RV apex base diameter (mm)	80±13	81±11	0.313
RV mid diameter (mm)	45±7	45±6	0.779
RV basal diameter (mm)	54±7	56±5	0.155
RV free wall thickness (mm)	6±2	5±1	0.591
RV end diastolic volume (ml)	204±48	200±48	0.295
RVEF (%)	39±6	40±6	0.788
RV stroke volume (ml)	79±16	80±18	0.430
LVEF (%)	56±6	59±9	0.396
LV stroke volume (ml)	83±26	76±20	0.308

*significant p-value; [a]*hemodynamically significant lesion at t = 1 or t = 2; bpm, beats per minute; BSA, body surface area; ccTGA, congenitally corrected transposition of the great arteries; CMR, cardiac magnetic resonance imaging; FAC, fractional area change; GLS, global longitudinal strain; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAPSE, mitral annular plane systolic excursion; NYHA, New York Heart Association; RV, right ventricle; RVEF, right ventricular ejection fraction; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TGA, transposition of the great arteries; TVP, tricuspid valve annuloplasty; TVR, tricuspid valve replacement; VSD, ventricular septal defect*.

As SR A and septal SR A (global and septal strain rate during late diastole, respectively) might be heart rate–dependent, analysis was repeated with correction for heart rate (using the partial correlations command in SPSS). After this correction, the correlations between SR A and RV CO and between septal SR A and LV SV were no longer significant. The correlation between FAC and RVEF was still apparent at T = 1 and just under the level of significance at T = 2. The correlation between GLS and RVEF was not altered by correction for heart rate (*Supplementary Table 9*). Of note, regarding systemic RV dimensions, the echocardiographic apex-base diameter showed consistent significant agreement with the CMR-derived apex-base diameter (ICC = 0.74 and p = 0.002 at T = 1; ICC = 0.62 and p = 0.009 at T = 2). The other dimensions (mid-diameter, base diameter, and wall thickness) did not show consistent significant agreement between echocardiographic and CMR measurements (*Supplementary Table 10*).

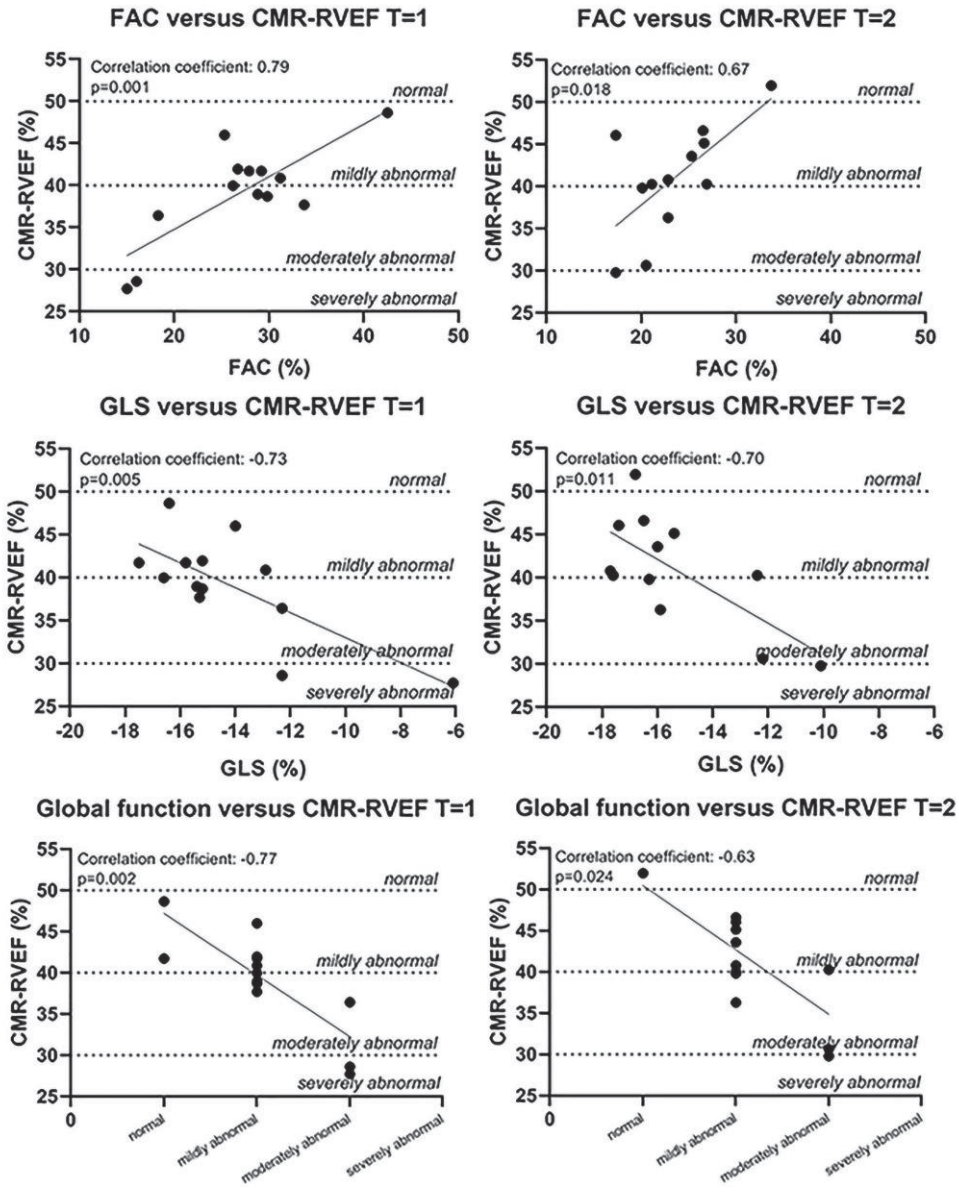

Figure 2: Correlations between echocardiographic variables and CMR-RVEF.
Normal values for MRI were based on reference values for the subpulmonary RV (32). CMR-RVEF, cardiac magnetic resonance imaging-derived (systemic) right ventricular ejection fraction; FAC, fractional area change; GLS, global longitudinal strain.

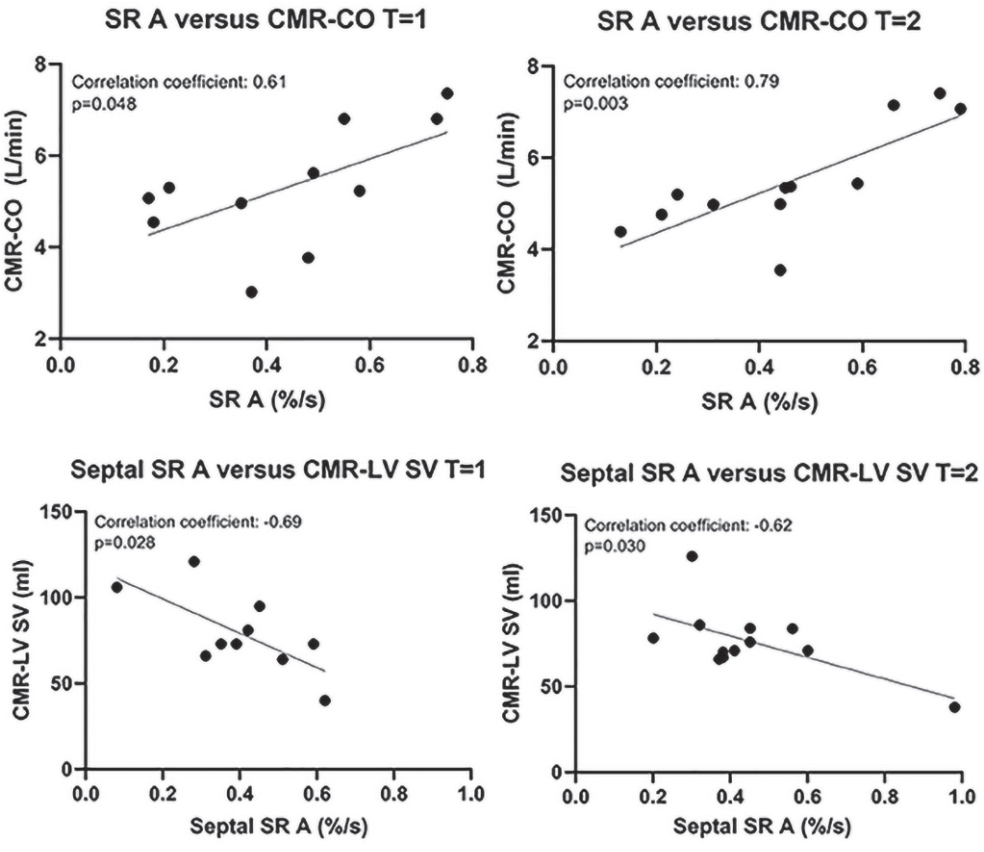

Figure 3: Correlations between echocardiographic and CMR variables other than RVEF.
CMR-CO, cardiac magnetic resonance imaging-derived cardiac output; CMR-LV SV, cardiac magnetic imaging-derived (subpulmonary) left ventricular stroke volume; SR A, maximal late diastolic strain rate.

The Influence of Tricuspid Regurgitation

To address the possible influence of tricuspid regurgitation (TR) on the assessment of systemic RV function, correlations were calculated between the degree of TR, global RV function, FAC, and GLS, and CMR-RVEF (*Supplementary Table 11*). No significant correlations were found.

Interobserver Agreement

The ICC for FAC is poor at T = 1 (ICC = 0.35, p = 0.196) and moderate at T = 2 (ICC = 0.70, p = 0.051). For GLS, the ICC is good at both time points (ICC = 0.82, p = 0.006, and ICC = 0.77, p = 0.024, respectively). The measurements of both observers are visualized in Bland–Altman plots (*Figure 4*). This visually confirms that the limits of agreement (dotted lines) of GLS seem acceptable although the limits of agreement of FAC seem moderately large.

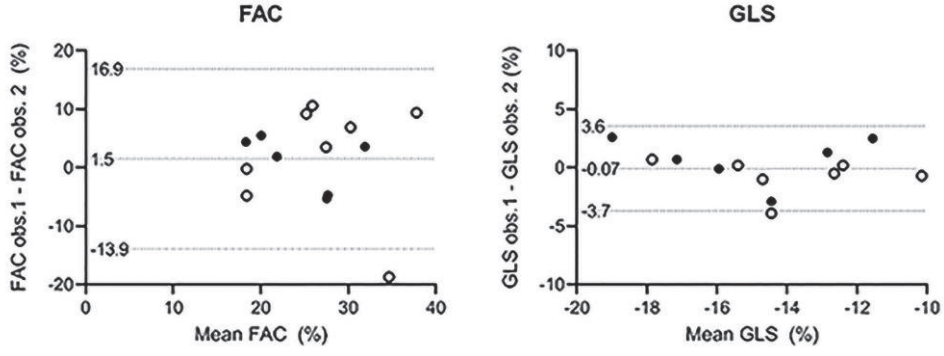

Figure 4

Bland–Altman plots. Open circles: T = 1. Filled circles: T = 2. The differences between the two observers are plotted on the y-axis and the mean value of the variable on the x-axis. The mean differences of all observations are close to zero in both cases, indicating no important bias between the two observers. No formal conclusion can be drawn from the constructed limits of agreement because measurements from the same patients at both time points are included. FAC, fractional area change; GLS, global longitudinal strain; obs., observer.

Interobserver agreement was also determined for each of the different ways of calculating the MPI. The MPI calculated from the TR curve and the RVOT signal was most reliable with ICC coefficients of 0.84 (p = 0.001) and 0.91 (p = 0.001), respectively. The other methods were considerably less reliable. None of the methods consistently correlated with CMR-RVEF, CO, or SV (see Supplementary Material).

Feasibility

From most echocardiograms, FAC (96%), GLS (96%), and (septal) SR A (both 93%) were successfully obtained. For RV dP/dt and LV end-diastolic diameter from the parasternal long axis image, the image quality was often insufficient. The older echocardiograms did not contain pulsed-wave TDI images, but measurements were possible in 10 out of the 14 echocardiograms at T = 2.

In addition, CMR-RVEF could not be determined in one patient at T = 1 and in one other patient at T = 2 because the raw images were no longer available.

Discussion

Key findings and context within literature

We aimed to identify reproducible echocardiographic variables that consistently correlated, i.e., at two points in time, with the gold standard of CMR-RVEF in a cohort of patients with systemic RV from daily clinical practice. The key findings are (*Figure* 5) that, in this cohort of patients with a systemic RV, (1) FAC, GLS, and global systemic RV function are consistently correlated with CMR-RVEF; (2) GLS shows a good interobserver agreement although the agreement is lower for FAC; (3) measurement of FAC and GLS is feasible in most cases (96%); and (4) other echocardiographic variables, including the MPI, IVA, TAPSE, and s' were not consistently correlated with CMR-RVEF.

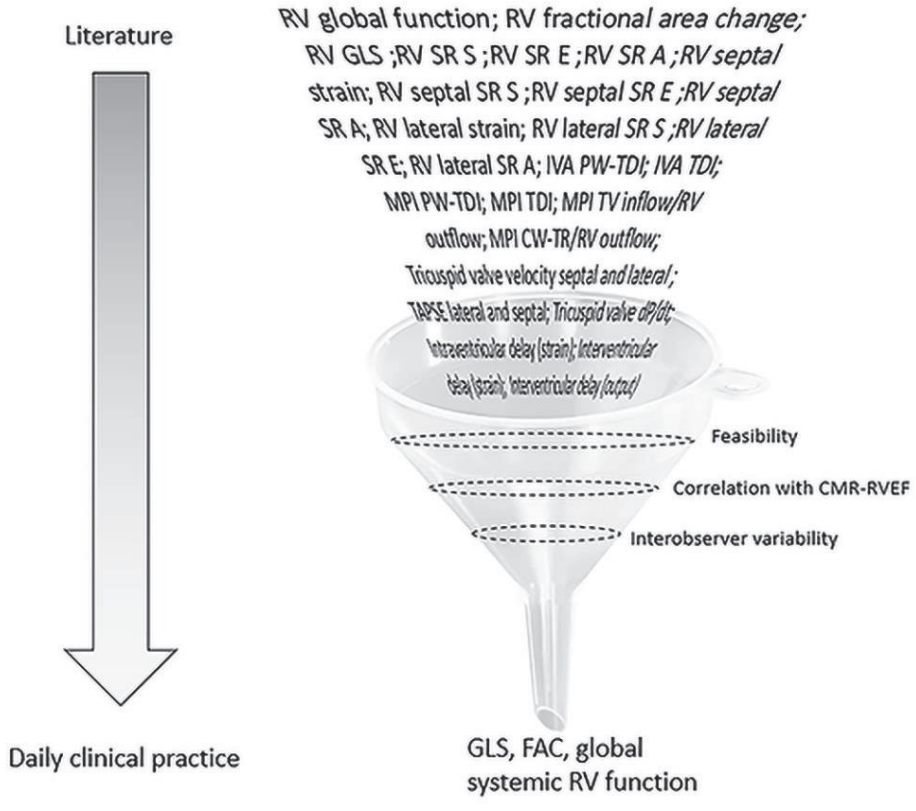

Figure 5

Graphical representation of selection of echocardiographic variables abstracted from literature to assess systemic RV function. FAC, fractional area change; GLS, global longitudinal strain; IVA, isovolumic acceleration; LV, left ventricle; MAPSE, mitral annular plane systolic excursion; MPI, myocardial performance index; PLAX, parasternal long-axis view; PW-TDI, pulsed-wave tissue doppler imaging; RV, right ventricle; SR A, maximal late diastolic strain rate; SR E, maximal early diastolic strain rate; SR S, maximal systolic strain rate; TAPSE, tricuspid annular plane systolic excursion.

To our knowledge, this is the first study to take a range of this extent of echocardiographic measurements of systemic RV function into account and to assess these for consistent correlation over two points in time. From these variables, FAC and especially GLS appear to be most useful. This is in line with previous work: Other studies consistently describe significant correlations between FAC and CMR-RVEF and GLS and CMR-RVEF although correlations between other echocardiographic variables and CMR-RVEF are less robust (11, 12, 14). Previous work also highlights the clinical relevance of FAC and GLS in patients with systemic RV. Lower FAC and higher (worse) GLS were associated with high-sensitive troponin T, a heart failure marker (33). Worse GLS was further associated with lower VO2max, heart failure, higher NYHA class, ventricular arrhythmias, and mortality (11, 12, 14, 15, 18, 21).

Estimation of the global RV function by visual assessment also correlated well with CMR. Although it is imprecise, it allows for an adequate first impression. Given the challenging echocardiographic windows in patients with a systemic RV, there is still is a place for visual assessment of the global systemic RV function in cases that do not allow quantification.

Measurement of GLS was more reliable than measurement of FAC. This is to be expected as it is difficult to exactly delineate the endocardial border of the systemic RV: Complex geometry, difficult delineation of the free wall, and the presence of trabeculations and a pronounced moderator band all contribute to this. Slight differences in delineation of the endocardial border between observers may lead to considerable differences in the calculated FAC. Previous studies demonstrate good interobserver agreement for GLS (11, 34) and fair to good agreement for FAC (35, 36). However, the interobserver agreement of FAC has not often been studied in systemic RV but rather in subpulmonary RV, which is easier to delineate. The strength of GLS is that the software shows how the drawn speckles move along with the respective myocardial segments during the cardiac cycle, and discrepancies can be adjusted before definitive calculation. In the case of FAC, checking whether the drawn end-diastolic outline and end-systolic outline actually follow the same contour is less straightforward.

We found no consistent significant correlations between CMR-RVEF and any type of MPI (also called TEI index). Previous studies show conflicting results (6, 9, 10, 16, 37). The reliability of the MPI is limited for each of its possible calculations: when calculated from the TR/pulsed wave signal of TV inflow and the doppler signal of the RVOT, a possible error is introduced due to a difference in heart rate between the two different images. When calculated from (pulsed wave)-TDI images, in which it may be difficult to

define the intervals, the measurement is imprecise. We also found no consistent significant correlations between CMR-RVEF and TAPSE, neither lateral nor septal. Previous studies show conflicting results (10, 19). TAPSE provides limited information because it measures local myocardial function. In the systemic RV, circumferential shortening may contribute more than longitudinal shortening compared with the subpulmonary RV, reducing the ability of TAPSE to reflect global systemic RV function (11). The same limitation may apply to s', which also shows no consistent correlation with RVEF.

Myocardial dyssynchrony is an important problem in patients with systemic RV, especially in patients receiving univentricular pacing (38). Resynchronization therapy is increasingly and successfully used (23, 30). Following previously published methodology, we calculated an intraventricular and an interventricular delay with measurements of the time to peak longitudinal strain in the RV free wall, the septum, and the LV free wall and calculated an interventricular delay from the times to start of output in the doppler signals of the RVOT and LVOT (*Supplementary Table 7*) (16, 19, 29, 30). Only one of these studies assessed the relation between these measures of dyssynchrony and CMR-RVEF and found a significant negative correlation (19). In the present study, however, we found no consistent correlations with CMR-RVEF. Possible explanations for this include that too few patients with considerable dyssynchrony were included in this cohort as few patients had a QRS duration>130 ms, that the optimal echocardiographic variable to identify dyssynchrony in patients with a systemic RV has yet to be identified, or that RVEF lacks correlation with dyssynchrony and can overestimate cardiac output in cases of dyssynchrony. Future studies correlating echocardiographic measures of dyssynchrony with invasive measurement of cardiac output as well as CMR-RVEF would be valuable.

The current data show no consistent correlation between dP/dt and CMR-RVEF. DP/dt reflects contractility: it assesses the time the systemic RV takes for the build-up of a certain level of pressure during isovolumic contraction and is, therefore, afterload independent. However, its measurement is highly subject to variation, especially with higher values.

Surprisingly, we found that SR A (late diastolic SR) was consistently positively correlated with CMR-cardiac output, and septal SR A was consistently negatively correlated with CMR-LV stroke volume. However, both of these correlations disappeared after correction for heart rate, possibly because a higher heart rate shortens diastolic filling time and generally increases diastolic strain rate. This may imply that strain rate measurements need to be corrected for heart rate.

In patients with a systemic RV, TR is a common consequence of systemic RV annulus dilation (39) and may lead to overestimation of systemic RV function. However, the present results do not show significant correlations between TR and the echocardiographic variables correlating with CMR-RVEF. Previous work in patients with a systemic RV additionally shows that TR was not correlated with CMR-RVEF (40). Although TR may also lead to overestimated systemic RV function as measured by CMR-RVEF, CMR-RVEF correlates well with clinical events in patients with a systemic RV (4, 5), and therefore, can still be used to assess systemic RV function regardless of TR.

Of note, although in this study no functional echocardiographic variables changed significantly over time, the RV apex-base diameter was significantly larger at T = 2. Also, the CMR and echocardiographic apex-base measurements show good agreement. This might indicate that RV lengthening may be a sensitive parameter of deterioration, which may be visible before the functional variables significantly deteriorate. This needs to be confirmed in larger studies.

Study Limitations

A considerable part of our cohort of patients with systemic RV did not meet the inclusion criteria regarding the availability of CMR and echocardiographic images, reflecting routine clinical practice but also limiting the sample size and introducing a possible selection bias causing patients with intracardiac devices to potentially be underrepresented. Furthermore, some correlation coefficients are based on a small sample size as their measurement was not feasible in a considerable number of cases. However, this reflects the practical applicability in routine clinical practice. Also, the interpretation of the RV wall thickness in the context of RV hypertrophy is limited as this requires short axis cine images unavailable in all but one patient. The measurements given were performed in four-chamber views, which is an inferior alternative. Last, the applicability of GLS is limited by variability introduced by spatial and temporal smoothing algorithms (although this affects segmental strain more than global strain, which we used) and by intervendor agreement (41). In this study, all measurements were performed in Echopac by GE Medical Systems.

Conclusion and Clinical Implications

In conclusion, from all echocardiographic variables available from literature, GLS appears to be the most robust variable to quantify systemic RV function over time. FAC can also be used well-provided that the endocardial border is traced in a consistent manner over time. In case no quantification of the systemic RV function can be made, visual assessment is an adequate substitute (*Figure 5*).

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Chapter 6

Clinical Course Long After Atrial Switch: A Novel Risk Score for Major Clinical Events

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Abstract

Background

Patients with transposition of the great arteries corrected by an atrial switch operation experience major clinical events during adulthood, mainly heart failure (HF) and arrhythmias, but data on the emerging risks remain scarce. We assessed the risk for events during the clinical course in adulthood, and provided a novel risk score for event-free survival.

Methods and Results

This multicenter study observed 167 patients with transposition of the great arteries corrected by an atrial switch operation (61% Mustard procedure; age, 28 [interquartile range, 24–36] years) for 13 (interquartile range, 9–16) years, during which 16 (10%) patients died, 33 (20%) had HF events, defined as HF hospitalizations, heart transplantation, ventricular assist device implantation, or HF-related death, and 15 (9%) had symptomatic ventricular arrhythmias. Five-year risk of mortality, first HF event, and first ventricular arrhythmia increased from 1% each at age 25 years, to 6% (95% CI, 4%–9%), 23% (95% CI, 17%–28%), and 5% (95% CI, 2%–8%), respectively, at age 50 years. Predictors for event-free survival were examined to construct a prediction model using bootstrapping techniques. A prediction model combining age >30 years, prior ventricular arrhythmia, age >1 year at repair, moderate or greater right ventricular dysfunction, severe tricuspid regurgitation, and mild or greater left ventricular dysfunction discriminated well between patients at low (<5%), intermediate (5%–20%), and high (>20%) 5-year risk (optimism-corrected C-statistic, 0.86 [95% CI, 0.82–0.90]). Observed 5- and 10-year event-free survival rates in low-risk patients were 100% and 97%, respectively, compared with only 31% and 8%, respectively, in high-risk patients.

Conclusions

The clinical course of patients undergoing atrial switch increasingly consists of major clinical events, especially HF. A novel risk score stratifying patients as low, intermediate, and high risk for event-free survival provides information on absolute individual risks, which may support decisions for pharmacological and interventional management.

Introduction

The atrial switch operation (AtrSO) significantly improved survival for patients with transposition of the great arteries (TGA), but left them with a challenging clinical course, including heart failure (HF), arrhythmias, and premature mortality.[1,2] Several studies have described late events up to the age of 30 to 40 years,[2,3] but accurate data on the emerging risks at older ages remain scarce. Furthermore, risk prediction remains difficult, as no models to predict absolute risks exist. New markers, such as B-type natriuretic peptide,[4] myocardial fibrosis,[5] and strain,[6] are mainly studied on an individual basis with short follow-up, whereas large long-term studies have mainly focused on characteristics from early childhood, such as TGA complexity or details of the repair surgery.[1,3,7] Accordingly, counseling adult patients is still difficult as knowledge on absolute individual risks of clinical events is limited. This hampers adequate management of the clinical course during adulthood,[8,9] because risk assessment at the individual level is needed to interfere timely in patients at highest risk without overtreating patients at limited risk. Therefore, this study aimed to provide insight in the incidence of mortality, HF, and ventricular arrhythmias (VAs) in adult patients with TGA long after AtrSO, uncover clinical predictors for event-free survival, and provide a risk score to improve patient counseling in daily clinical practice.

Methods

Using the Dutch CONCOR registry, which includes adults (aged ≥18 years) with congenital heart disease, we assessed survival and risk of events in adult patients with TGA after AtrSO. The CONCOR registry conforms to the Declaration of Helsinki, and was approved by the ethics boards of all participating centers.[10] The data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population and Data Collection

This study consisted of patients included in the CONCOR registry in 5 tertiary medical centers with simple or complex TGA (defined as TGA with concomitant ventricular septal defect, left ventricular (LV) outflow tract obstruction, or coarctation of the aorta) after AtrSO. Patients were followed up from the first hospital visit after written informed consent for inclusion in the CONCOR registry (earliest inclusion in 2001) until 2019, heart transplantation, ventricular assist device implantation, or death. Medical records were reviewed for baseline and follow-up data on events, clinical status, described as New York Heart Association functional class, ECGs, imaging (echocardiography, cardiovascular magnetic resonance, and computed tomography) and exercise testing performed during routine follow-up. Echocardiographic systemic

right ventricular (RV) and subpulmonary LV function levels were visually graded by cardiologists at each participating center as normal or mildly, moderately, or severely impaired.[11] Tricuspid regurgitation (TR) severity was graded, according to the European guidelines, from absent/trivial to severe TR.[12] Baffle obstruction was suspected in case of flow velocity of >1.5 m/s, turbulence, or loss of biphasic flow in the conduits.[11]

Outcome Definitions

Clinical events were scored, specifically (1) HF events, defined as hospitalizations for HF, heart transplantation, ventricular assist device implantation, or HF as cause of death; (2) VAs, defined as symptomatic nonsustained VA, sustained VA, and sudden death; and (3) all-cause mortality.

The primary end point used in prediction analysis was time to the first event of the composite of HF events, arrhythmia events, and all-cause mortality.

In addition, RV dysfunction, defined as moderate or greater RV dysfunction on echocardiography, and New York Heart Association functional class at last follow-up were reported to analyze clinical decline during adulthood.

Statistical Analysis

Data are expressed as numbers (percentages), mean±SD, or median (interquartile range), as appropriate. Kaplan-Meier analysis with age as a time scale, using a delayed entry method for left-truncated, right-censored data, was conducted to provide survival estimates of event-naive patients.[13,14] Five-year risk of first events was estimated using discrete-time survival methods.

Multiple imputation, based on baseline characteristics (maximum percentage missing, 29%) and the end points, was used to address missing data, creating 100 data sets. Characteristics derived from cardiovascular magnetic resonance/computed tomography and cardiopulmonary exercise tests were not included in the imputation models, because they entailed many missing values (54%–61%) as they were performed less frequently during routine follow-up, especially in the earlier years. Cox proportional hazards regression was used to analyze whether patient characteristics were associated with event-free survival.

Prediction Model

A prediction model based on clinical characteristics, ECG, and echocardiography measurements at baseline was derived with backward stepwise selection based on the Akaike Information Criterion, in 100 bootstrap samples per imputed data set. Entry criterion into multivariable analysis was P<0.05 in univariable analysis. Of highly correlated characteristics (symptoms/prior HF hospitalization, prior VA/implantable cardioverter-defibrillator [ICD], and pacemaker/ventricular pacing), the variable with highest C-statistic in univariable analysis was included in multivariable analysis. Age was kept in all models because of its clinical significance. Continuous variables that had a nonlinear relation with the outcome were dichotomized on the basis of individual receiver operating characteristic curves. Variables selected in >60% of the bootstrap samples of >60% of the imputed data sets were included in the final prediction model[15,16] (*Table S1*). Risk factors were awarded score points based on the β in the final model. Internal validation was performed using bootstrapping techniques, assessing model calibration using the calibration slope and model discrimination using the optimism-corrected C-statistic penalized for overfitting.

Statistical analyses were performed in RStudio V.1.1.453 (RStudio Team, Boston, MA) using R-version 3.6.1 (R Core Team, Vienna, Austria), with the mice,[17] survival,[18] and bootStepAIC[19] packages. P<0.05 was considered statistically significant.

Results

Baseline Characteristics

In total, 167 patients with TGA after atrial switch were included (62% men; 61% Mustard procedure; median age, 28 [interquartile range, 24–36] years at inclusion) (baseline characteristics in *Table 1*). At inclusion, 28 (17%) used β blockers, 45 (27%) used angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 14 (8%) used diuretics.

Table 1: Baseline Characteristics and Univariable Cox Regression for Event-Free Survival

Characteristics	All Patients (n=167)	Patients With Events (n=41)	HR (95% CI)	P Value
Clinical characteristics				
Aged >30 y	74 (44)	30 (73)	5.21 (2.59–10.5)	<0.001
Men	104 (62)	22 (54)	0.73 (0.40–1.36)	0.33
Complex TGA	51 (31)	16 (39)	1.61 (0.86–3.02)	0.14
Mustard procedure	101 (61)	35 (85)	5.16 (2.16–12.3)	<0.001
Aged >1 y at AtrSO	89 (53)	36 (88)	8.40 (3.29–21.4)	<0.001
Symptoms (NYHA functional class ≥2) (n=162)	39 (25)	16 (41)	2.97 (1.56–5.67)	0.001
Body mass index, kg/m2 (n=159)	24±5	25±6	1.06 (1.00–1.12)	0.058
Systolic blood pressure, mm Hg (n=160)[a]	121±14	118±12	0.88 (0.69–1.12)	0.29
Prior heart failure hospitalization	8 (5)	6 (15)	8.61 (3.53–21.0)	<0.001
Prior ventricular arrythmia	13 (8)	9 (22)	4.23 (2.01–8.90)	<0.001
Prior baffle procedure	26 (16)	7 (17)	1.54 (0.68–3.50)	0.30
ICD	5 (3)	3 (7)	4.72 (1.45–15.4)	0.010
Pacemaker	41 (25)	17 (42)	2.91 (1.56–5.45)	<0.001
Prior supraventricular tachyarrhythmia	58 (35)	21 (51)	2.12 (1.15–3.91)	0.017
ECG				
Heart rate, /min (n=138)[a]	68±15	73±15	1.31 (1.07–1.60)	0.009
QRS duration >120 ms (n=118)	31 (26)	16 (53)	4.50 (2.29–8.81)	<0.001
Loss of sinus rhythm (n=163)	42 (26)	12 (29)	1.30 (0.66–2.56)	0.45
Ventricular pacing	17 (10)	8 (20)	2.83 (1.30–6.15)	0.009
Echocardiography				
Moderate or greater impairment of RV function (n=157)	38 (24)	17 (43)	4.08 (2.11–7.90)	<0.001
Severe tricuspid regurgitation (n=159)	12 (8)	10 (24)	7.00 (3.24–15.1)	<0.001
Mild or greater	8 (5)	6 (15)	7.16 (2.80–18.3)	<0.001

impairment of LV function (n=162)				
Signs of baffle obstruction (n=154)	27 (18)	6 (16)	0.94 (0.39–2.28)	0.90
CMR/CT				
LVEDV, mL (n=67)[a]	142±45	137±30	1.06 (0.95–1.18)	0.32
LVESV, mL (n=65)[a]	63±25	61±16	1.14 (0.97–1.34)	0.12
LVEF, % (n=67)	57±9	56±7	0.97 (0.92–1.01)	0.17
RVEDV, mL (n=76)[a]	209±65	223±59	1.08 (1.01–1.15)	0.015
RVESV, mL (n=73)[a]	120±49	133±46	1.10 (1.03–1.18)	0.007
RVEF, % (n=76)	42±9	40±6	0.96 (0.91–1.01)	0.082
Exercise testing				
Peak heart rate, /min (n=68)[a]	169 (150–184)	157 (127–174)	0.86 (0.74–1.00)	0.049
Peak systolic blood pressure, mm Hg (n=62)[a]	170±31	166±32	1.01 (0.88–1.16)	0.88

Data described as frequency (percentage), mean±SD, or median (interquartile range). AtrSO indicates atrial switch operation; CMR, cardiovascular magnetic resonance; CT, computed tomography; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; NYHA, New York Heart Association; RV, right ventricular; RVEDV, RV end-diastolic volume; RVEF, RV ejection fraction; RVESV, RV end-systolic volume; and TGA, transposition of the great arteries. [a]HR per 10-unit increase.

Clinical Course

Patients were prospectively followed for a median of 13 (interquartile range, 9–16) years, with a median age at last follow-up of 41 (interquartile range, 36–46) years. Fourteen patients were followed up over the age of 50 years. During follow-up, 30 (18%) patients were hospitalized for HF, heart transplantation was performed in 2 patients, 3 patients got a ventricular assist device as destination therapy, and 15 (9%) patients had VAs. In total, 16 (10%) patients died (7 of HF, 5 sudden deaths, 3 of other cardiac causes, and 1 noncardiac death) (distribution of events in *Table 2*). Forty-one (25%) patients reached the primary end point, with a median event-free survival of event-naive patients surviving into adulthood of 50 years (Kaplan-Meier curves in *Figure S1*). Median survival until death or transplant/ventricular assist device of adults with TGA after atrial switch was 54 years. Risks of first HF event, first arrhythmia, and mortality were all only 1% at the age of 25 to 30 years. At the age of 50 to 55 years, this increased to 23% (95% CI, 17%–28%), 5% (95% CI, 2%–8%), and 6% (95% CI, 4%–9%), respectively (*Figure 1*). In the age group 30 to 40 years, 30% were diagnosed to have moderate or greater RV dysfunction, which increased to 49% for those aged between 40 and 50 years and to 53% for those aged >50 years. Symptoms of HF were present in

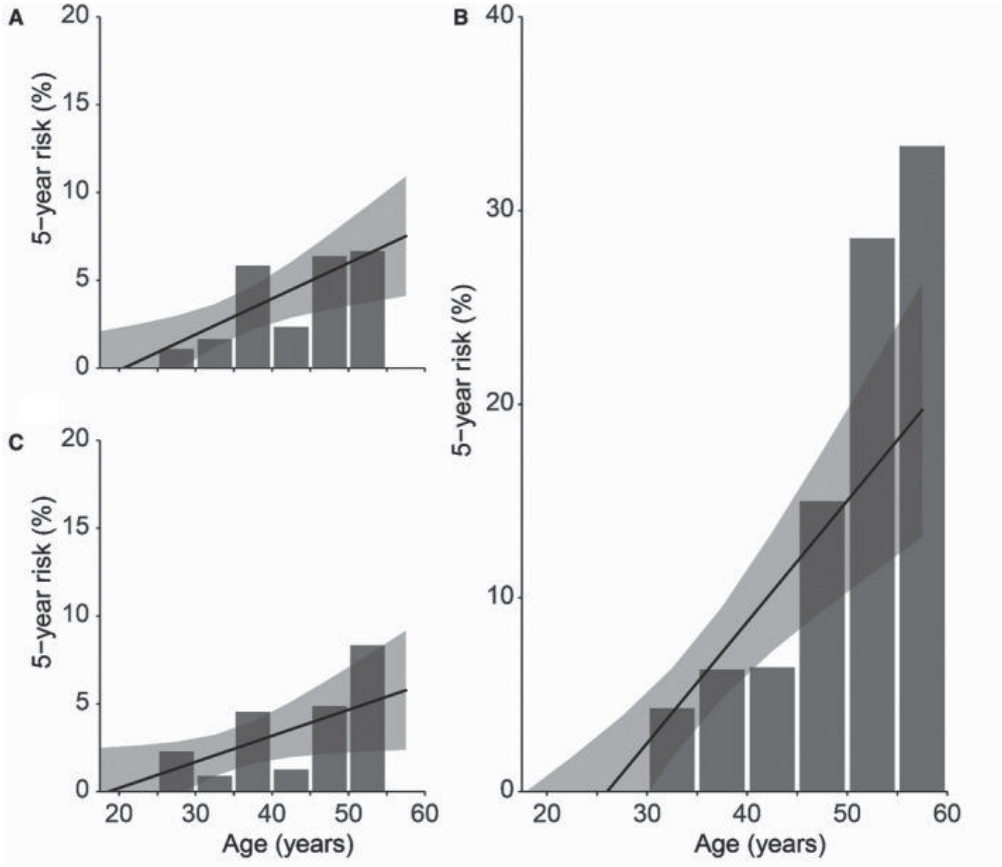
22% of the patients aged 30 to 40 years, in 52% of patients aged 40 to 50 years, and in 67% of patients aged >50 years. In line with clinical deterioration, a subset of patients underwent interventions during follow-up (22 baffle and 10 tricuspid interventions).

Table 2: Distribution of Events

Variable	Patients With Event, N	Included in Primary End Point, N[a]
(A) Event-free survival (primary end point)	41	
(B) All scored events		
Heart failure	33	
Heart failure hospitalization	30	25
HTX/VAD	5	2
Heart failure as cause of death	7	1
Ventricular arrhythmia	15	
Symptomatic nonsustained VT	4	4
Sustained VT	5	3
Ventricular fibrillation	4	3
Cardiac arrest/sudden death[b]	5	2
All-cause mortalty	16	
Heart failure	7	
Sudden death	5	
Other cardiac	3	
Noncardiac death	1	1

(A) Number of patients who reached the primary end point. (B) Number of patients per subtype of scored events. Numbers of subtypes do not add up to the event total as patients may have had multiple subtypes of events (eg, heart failure hospitalization and subsequently HTX). HTX indicates heart transplantation; VAD, ventricular assist device; and VT, ventricular tachycardia.

[a]In patients with multiple events, the first event was included in the primary end point. Heart failure–related and sudden deaths were scored under heart failure and ventricular arrhythmia, respectively. [b]Cardiac arrest with unclear underlying rhythm from patient records or unexplained sudden death.



N. at risk

Age	*<20*	*20-25*	*25-30*	*30-35*	*35-40*	*40-45*	*45-50*	*50-55*	*55+*
A Mortality	13	54	91	121	120	85	47	15	3
B Heart failure	13	52	87	116	111	78	40	14	3
C VA	12	50	87	111	110	79	41	12	1

Figure 1: Five-year risk of first events.

Five-year risk of all-cause mortality (A), first heart failure event (B), and first ventricular arrhythmia (VA) event (C). The bars show the observed incidence in percentage of patients at risk per age group, and the black line shows the predicted risk based on the observed incidences, assuming a linear model. N. indicates number.

Risk Predictors

Table 1 lists univariable associations between baseline characteristics and event-free survival. Multiple characteristics were significant predictors in univariable analysis, including age, surgical type, age at AtrSO, symptoms, history of supraventricular arrhythmias or VAs, heart rate, QRS duration, echocardiographic measures of RV function, LV function, and TR, and peak heart rate during exercise. RV volumes, measured by cardiovascular magnetic resonance/computed tomography, were also significantly associated with event-free survival.

Prediction Model

Table 3 shows the results of multivariable Cox regression analysis and the final prediction model, which included age >30 years, age >1 year at AtrSO, prior VA, moderate or greater RV dysfunction, severe TR, and mild or greater LV dysfunction (score chart in *Figure 2A*). The risk model satisfied the proportional hazard assumption, had a calibration slope of 0.97 (95% CI, 0.74–1.19) (*Figure S2*), and discriminated well between patients who did and did not reach the primary end point (optimism-corrected C-statistic, 0.86 [95% CI, 0.82–0.90]). Patients were categorized into low, intermediate, and high risk, with 5-year predicted risk of events of <5%, 5% to 20%, and >20%, respectively (*Figure 2B*). In patients with a 5-year predicted risk of <5% (score points ≤2; n=91 [54%]), observed event-free survival was 100%, 97%, and 94% after 5, 10, and 15 years of follow-up, respectively (*Figure 2C*). Risk for events was significantly increased in patients with higher scores (hazard ratio [HR], 10.5 [95% CI, 4.0–27.9] [P<0.001]; and HR, 87.7 [95% CI, 29.0–265.4] [P<0.001] for intermediate and high risk, respectively). Event-free survival was 90% and 72% at 5- and 10-year follow-up, respectively, in intermediate-risk patients (score points 2.5–3.5; n=62 [37%]). In high-risk patients, with predicted 5-year risk of >20% (score points ≥4; n=14 [8%]), observed 5- and 10-year event-free survival was only 32% and 8%, respectively. The model also performed well for prediction of all-cause mortality alone (optimism-corrected C-statistic, 0.89 [95% CI, 0.82–0.95]), with observed 10-year survival of 100%, 90%, and 37% in the low-, intermediate-, and high-risk groups, respectively (*Figure S3*). Apart from the independent risk factors, patients at high and intermediate predicted risk more often had HF symptoms, ICD or pacemaker devices, and prior supraventricular tachyarrhythmias compared with patients in the low-risk group (*Table S2*).

Table 3: Multivariable Prediction Model and Score Points for Event-Free Survival

	Full Model		Final Model		
Predictors	HR (95% CI)	P Value	HR (95% CI)	P Value	Points
Aged >30 y	1.95 (0.79–4.77)	0.15	2.75 (1.20–6.29)	0.017	1
Mustard procedure	1.90 (0.71–5.07)	0.20			
Aged >1 y at AtrSO	4.82 (1.64–14.2)	0.004	4.58 (1.64–12.8)	0.004	1.5
Symptoms (NYHA functional class ≥2	1.90 (0.88–4.11)	0.11			
Prior ventricular arrhythmia	4.65 (1.80–12.0)	0.001	2.89 (1.22–6.81)	0.015	1
Pacemaker	0.65 (0.24–1.73)	0.38			
Prior supraventricular arrhythmia	0.54 (0.24–1.20)	0.13			
QRS duration >120 ms	1.93 (0.76–4.89)	0.17			
Heart rate, beats/min	1.07 (0.81–1.41)	0.64			
Moderate or greater RV dysfunction	2.78 (1.16–6.64)	0.021	2.79 (1.35–5.75)	0.005	1
Severe tricuspid regurgitation	3.56 (1.25–10.2)	0.018	3.55 (1.40–9.01)	0.008	1.5
Mild or greater LV dysfunction	3.32 (1.16–9.46)	0.025	4.46 (1.70–11.7)	0.002	1.5

Of highly correlated characteristics (symptoms/prior heart failure hospitalization, prior ventricular arrhythmia/implantable cardioverter-defibrillator, and pacemaker/ventricular pacing), the variable with highest C-statistic in univariable analysis was included in multivariable analysis. Variables selected in >60% of the bootstrap samples of >60% of the imputed data sets (Table S1) were included in the final prediction model. AtrSO indicates atrial switch operation; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association; and RV, right ventricular.

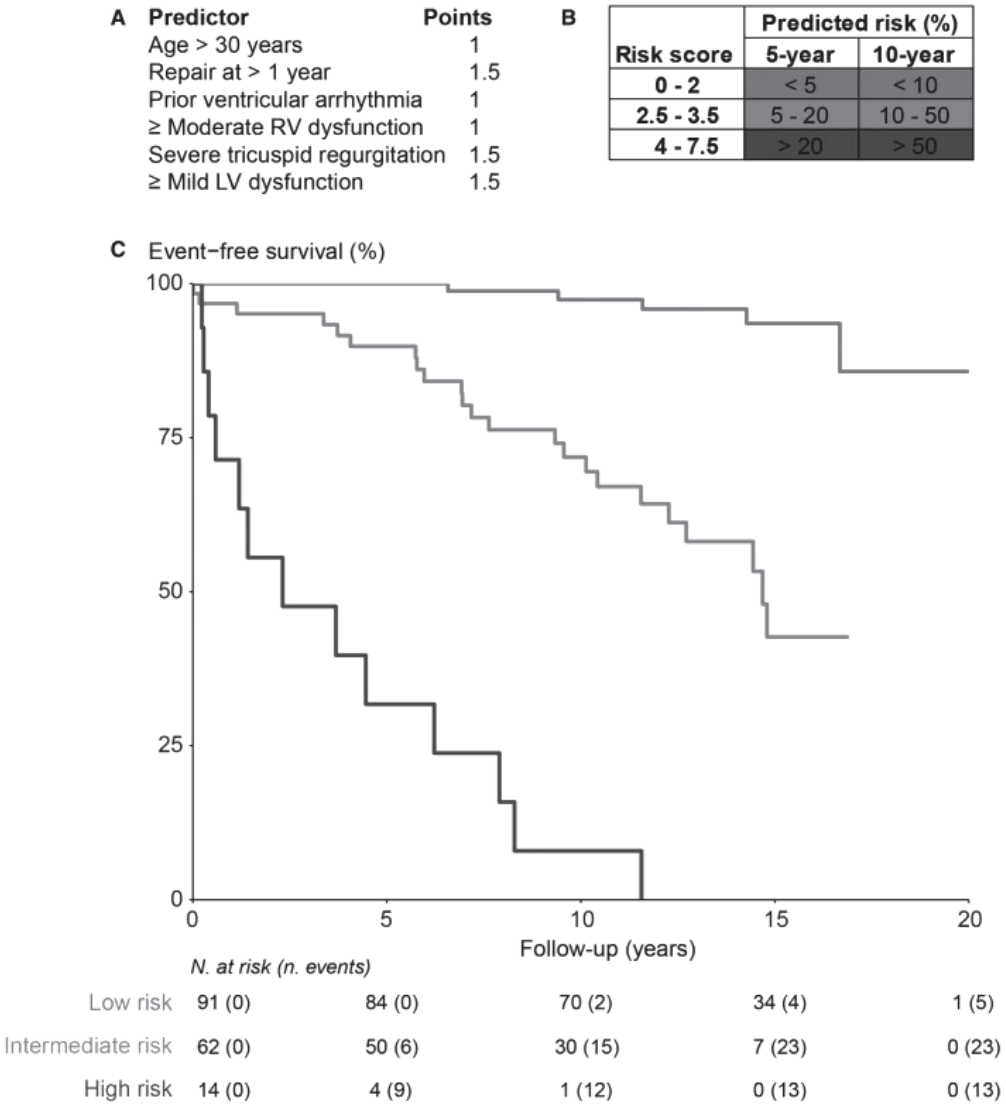


Figure 2: Observed event-free survival by predicted risk category.
A, Score points of the risk model. B, Predicted risk for the combined end point (heart failure, ventricular arrhythmias, and mortality) based on the risk score. C, Observed event-free survival of patients with predicted low (<5% in 5 years), intermediate (5%–20% in 5 years), and high risk (>20% in 5 years). LV indicates left ventricular; N., number; and RV, right ventricular.

Discussion

This large cohort study with comprehensive patient characteristics and long-term follow-up provides estimates of absolute risks of major events during the clinical course of adults after AtrSO. To our knowledge, this is the first study presenting a practical risk score based on multiple markers that can easily be obtained during routine outpatient visits, stratifying adult patients undergoing AtrSO into low-, intermediate-, and high-risk groups.

Clinical Course

We present absolute risks of major clinical events during adulthood, up to the sixth decade of life. This expands current knowledge on population-level relative risks and of studies including children to the present adult population on an individual basis. As illustrated in *Figure* 3, asymptomatic RV dysfunction was already present within the third decade of life, whereas more than half of patients in their fourth and fifth decade experience HF symptoms. A continuously increasing portion of patients have major clinical events with older age. In line with previous work, most major events at young adult age consisted of VAs and sudden death, but after the age of 40 years, HF prevalence had increased, and concurrently HF-related death became the major cause of death.[20,21] Because the AtrSO was largely abandoned in favor of the arterial switch in the 1980s, most of the worldwide population with TGA who underwent AtrSO will be 40 to 60 years old in the coming decade. For both patients and physicians, risk assessment for the individual patient is needed to discriminate between patients at risk, who might benefit from intensive medical care and clinical interventions, and patients who can have a more relaxed regimen. The clinical tools provided in this study will be useful to support decisions on prevention and treatment of the prevailing complications.

Prediction Model

Currently, management of patients with TGA corrected by an AtrSO is hampered by the lack of evidence-based recommendations.[8,9] Randomized clinical trials are difficult to perform because of the limited population size. Second best are large cohort studies investigating outcomes and providing tools for risk assessment. Our study is the first to provide a risk score that can help to counsel patients and guide clinicians in their management strategies. Compared with previously published general risk models for sudden death[22] and HF[23] in adults with congenital heart disease, the presented model adds TGA-AtrSO–specific information (ie, age at AtrSO repair and TR severity). The model discriminated well between patients at low, intermediate, and high risk for both the composite of major clinical events and all-cause mortality alone.

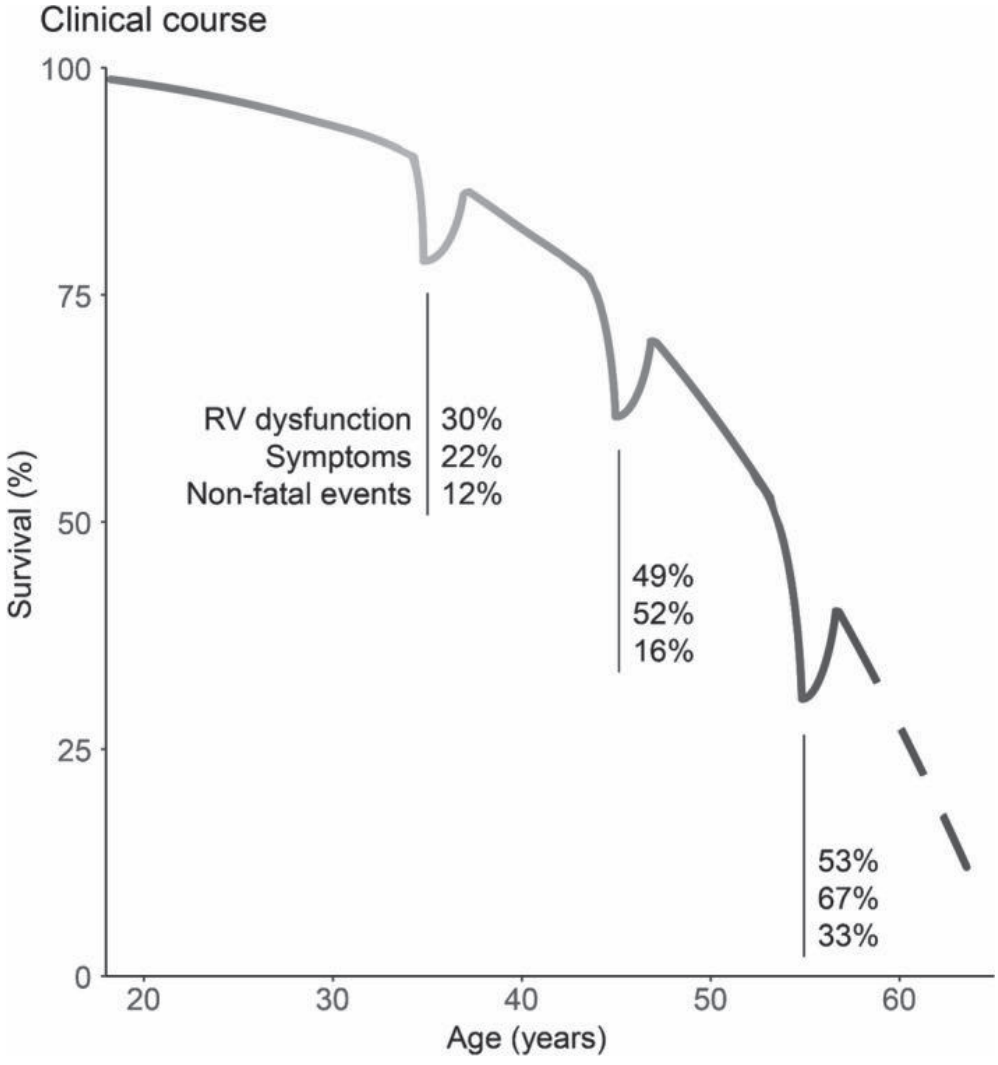


Figure 3: Clinical course during adulthood in patients undergoing atrial switch.
Illustration based on survival during adulthood of patients undergoing atrial switch in the CONCOR registry.[13] The percentage of patients with right ventricular (RV) dysfunction (defined as moderate or greater RV dysfunction on echocardiography), symptoms, and nonfatal clinical events (heart failure hospitalizations, transplant/ventricular assist device implantation, and symptomatic ventricular arrhythmias) is depicted for the third, fourth, and fifth decade of life. The dips in the curve signify the percentage of surviving patients enduring nonfatal clinical events during the decade. The figure illustrates that both morbidity and mortality rates are increasing as these patients grow older.

The low-risk group comprised 54% of patients who experienced no clinical events during the first 5 years of follow-up. Moreover, during a median of 13 years of follow-up, only 5 events occurred. The low-risk patients were mostly young, with only mild RV dysfunction and no HF symptoms. Current US guidelines advise yearly outpatient visits in all patients with TGA corrected by an AtrSO, even those without symptoms,[9] but it seems justified to prolong the regular follow-up interval (eg, to 2 years) and defer medical treatment with uncertain benefit in these low-risk patients.

One third of patients comprised the intermediate-risk group, with a 5-year event-free survival of 90%. In these patients, management considerations to improve event-free survival should be considered on an individual basis (eg, yearly follow-up with imaging for timely identification of RV deterioration and initiation of angiotensin-converting enzyme inhibition to prevent clinical HF when symptoms appear).[24] In select cases, ICD implantation or tricuspid valve surgery may be considered. Indeed, severe TR largely contributed to the risk of events, in line with prior research.[1,4,25,26,27] TR is usually secondary to annular dilatation and may further aggravate RV dysfunction. Tricuspid valve replacement can stabilize RV function and improve functional class for several years, but timely consideration is crucial, as reduced ejection fraction of the systemic RV is a major risk factor for surgical mortality.[28]

Of patients, 8% were identified as high-risk patients, with an event-free 5-year survival of only 56%. Moreover, 30% had events within 1 year, and mortality was >50% within 10 years of follow-up. These findings stress that a comprehensive clinical evaluation with frequent follow-up (eg, every 6 months) is indicated in these patients. Within 10 years of follow-up, 6 of the 14 high-risk patients had had VAs. Guidelines recommend ICD implantation in patients with advanced systemic RV dysfunction, especially in presence of nonsustained VA, HF symptoms, or severe TR.[8,29] As most high-risk patients meet these criteria, the presented risk model underscores that ICD implantation should be considered in these patients at highest risk. Supraventricular tachyarrhythmias and prolonged QRS duration, which have previously been associated with sudden death,[22,26,30,31] may also be acknowledged in the judgement for ICD therapy. Prior supraventricular tachyarrhythmias and QRS duration >120 ms were associated with our primary end point in univariable analysis. Yet, these variables did not improve the presented multivariable model, probably as 68% of our primary end point events concerned HF instead of VA. Large registries of patients with TGA corrected by an AtrSO will improve identification of those who will benefit most from ICD implantation.

HF was especially prevalent from the fourth decade on. Cardiac resynchronization therapy could be considered to decrease the contribution of dyssynchronous myocardial contractions to progressive RV failure, especially in patients with long QRS duration.[32,33] Progressive backward failure of the RV can also lead to dysfunction of the LV, although it is anatomically suited to sustain high pressures. Therefore, patients with overt LV dysfunction appeared to be already far down the path of deterioration. In all high-risk patients, HF medication and timely referral for transplantation or assist device should be considered to decrease risk of premature (HF-related) death.

Methodological Issues

Limitations inherent to the observational design include follow-up of a selected group of patients in tertiary medical centers, with visually graded data on ventricular function as clinically customary. Evaluating the effect of interventions during follow-up and assessing the pathogenesis of the risk model and RV deterioration were not part of our study. The sample size was limited to 167 patients, with only 41 reaching the primary end point. Although we could not perform external validation, this risk model was based on multicenter data and performed well after model stability analysis and internal validation, which is a reliable estimate of good external predictive performance.[34] We focused on robust end points that are consistently recorded in patient records. This strengthens the risk model, as it predicts major events, instead of preceding events, such as supraventricular arrhythmias. We did not study new markers, such as NT-proBNP (N-terminal pro-B-type natriuretic peptide), as these were acquired less often in the earlier eras, because we preferred long-term prediction on robust outcomes over short-term follow-up with new markers. Future studies may determine whether additional measurements, such as blood biomarkers, myocardial strain, or myocardial fibrosis on cardiovascular magnetic resonance, have added value in risk stratification.[6,25,35,36]

Conclusions

The current study provides an easily applicable clinical risk model that identifies patients at low, intermediate, and high absolute risk of major clinical events. The resulting individual risk stratification can assist in counseling patients about their risk, help determine follow-up intensity, and support decisions on invasive strategies or pharmacological treatment, thereby aiding clinicians to improve the clinical course of patients with TGA corrected by an AtrSO.

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Chapter 7

Sacubitril/valsartan in the treatment of systemic right ventricular failure

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Abstract

Objective

Pharmacological options for patients with a failing systemic right ventricle (RV) in the context of transposition of the great arteries (TGA) after atrial switch or congenitally corrected TGA (ccTGA) are not well defined. This study aims to investigate the feasibility and effects of sacubitril/valsartan treatment in a single-centre cohort of patients.

Methods

Data on all consecutive adult patients (n=20, mean age 46 years, 50% women) with a failing systemic RV in a biventricular circulation treated with sacubitril/valsartan in our centre are reported. Patients with a systemic RV ejection fraction of ≤35% who were symptomatic despite treatment with β-blocker and ACE-inhibitor/angiotensin II receptor-blockers were started on sacubitril/valsartan. This cohort underwent structural follow-up including echocardiography, exercise testing, laboratory investigations and quality of life (QOL) assessment.

Results

Six-month follow-up data were available in 18 out of 20 patients, including 12 (67%) patients with TGA after atrial switch and 6 (33%) patients with ccTGA. N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) decreased significantly (950–358 ng/L, p<0.001). Echocardiographic systemic RV fractional area change and global longitudinal strain showed small improvements (19%–22%, p<0.001 and –11% to –13%, p=0.014, respectively). The 6 min walking distance improved significantly from an average of 564 to 600 m (p=0.011). The QOL domains of cognitive function, sleep and vitality improved (p=0.015, p=0.007 and p=0.037, respectively).

Conclusions

We describe the first patient cohort with systemic RV failure treated with sacubitril/valsartan. Treatment appears feasible with improvements in NT-pro-BNP and echocardiographic function. Our positive results show the potential of sacubitril/valsartan for this patient population.

Introduction

Patients with transposition of the great arteries (TGA) who underwent an atrial switch procedure according to Mustard or Senning constitute an important group within the clinical setting of adult patients with congenital heart disease. Together with patients with congenitally corrected transposition of the great arteries (ccTGA), they represent a cohort of patients with a systemic right ventricle (RV)—a situation in which the morphological RV is in subaortic position and sustains the systemic circulation. Although mid-term survival in this group is good, failure of the systemic RV is, in the long term, inevitable.[1, 2] Furthermore, tricuspid valve regurgitation (TR), conduction abnormalities, arrhythmias and myocardial perfusion defects are frequently encountered and complicate the course of heart failure in these patients.[1, 2]

Compared with treatment of systolic heart failure in patients with a systemic left ventricle (LV), pharmacological options in patients with a systemic RV are currently less well defined. Data regarding effectiveness of drug therapy in the latter group are scarce and extrapolation from the guidelines and recommendations on LV failure is inappropriate due to specific anatomic and haemodynamic characteristics of the systemic RV. Although beta-blockers provide beneficial effects at higher doses, this may result in clinically important bradycardia in the atrioventricular conduction abnormalities prone patients with ccTGA.[3] Beta-blockers and ACE inhibitors (ACEi)/angiotensin II-receptor blockers (ARB) are prescribed based on carefully optimistic results from several, mostly small, trials and retrospective studies.[4–9]

The largest trial regarding medical treatment of the failing systemic RV investigated the effects of valsartan in 88 patients with congenitally or by an atrial switch corrected TGA.9 In symptomatic patients in the placebo group, the RV ejection fraction deteriorated significantly, whereas in the valsartan group, the ejection fraction remained stable over 3 years of follow-up. Longer follow-up of this cohort showed fewer events in symptomatic patients in the valsartan group,[10] suggesting that adequate medical therapy can impact the long-term outcomes in patients with systemic RV failure.

The treatment of symptomatic systolic LV heart failure has improved since the introduction of the combination drug sacubitril/valsartan, resulting in positive effects in clinical outcomes as well as in beneficial structural and functional cardiac changes.[11] The combination of sacubitril and valsartan was superior to enalapril in reducing the risk of death and hospitalisation for systolic heart failure of patients with acquired heart disease, all with a systemic LV.[11]

Neurohormonal activation has been shown to be related to symptom severity and systemic ventricular dysfunction in patients with congenital heart disease.[12] In patients with a systemic RV, the N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) levels have a predictive value in clinical end points, including mortality.[13, 14] Furthermore, brain natriuretic peptide (BNP) has been shown to correlate with systemic RV dysfunction.[15] Sacubitril is a neprilysin inhibitor. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides and bradykinin, but not NT-pro-BNP. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that leads to vasoconstriction, sodium retention and maladaptive remodelling in heart failure. Although BNP and NT-pro-BNP have both been proven to be useful biomarkers, the levels of BNP often fluctuate during heart failure therapy (attributable to inhibition of neprilysin), whereas decrease in NT-pro-BNP levels has been correlated with improvements in heart failure condition. This could lead to clinical confusion and the use of NT-pro-BNP has been preferred and recommended.[11, 16–18]

Sacubitril/valsartan treatment is currently indicated in all symptomatic patients with heart failure with an ejection fraction ≤35% already treated with a β-blocker and an ACEi or ARB.[19] However, no studies are yet available evaluating the effects of sacubitril/valsartan on heart failure in the systemic RV population. The current study aims to investigate the feasibility and effects of sacubitril/valsartan treatment in this group of patients in a single-centre cohort.

Methods

Design and inclusion/exclusion criteria

In this single-centre (Leiden University Medical Center) cohort study, data of all consecutive adult patients with a failing systemic RV in a biventricular circulation treated with sacubitril/valsartan are reported. In 2018, all adult patients with systemic RV heart failure (n=67) were screened for eligibility for treatment with sacubitril/valsartan. Those who had an (estimated) systemic RV ejection fraction of ≤35% (defined as a moderately to severely reduced systemic RV function on echocardiography and/or MRI) and remained symptomatic despite treatment with highest tolerated doses of a β-blocker and an ACEi or ARB for a period of at least 3 months were advised to start treatment with sacubitril/valsartan.[11] Symptoms were assessed based on the history and complaints as reported at the outpatient clinic (including the patients' performance during work and sport activities) and/or heart failure related admissions or ambulant medication adjustments (increasing diuretic

dose to remain euvolemic). Patients with a ventricular assist device (VAD) or awaiting the implantation of a VAD, or severe renal function impairment (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2) were excluded.

Treatment and follow-up

Before the initiation of sacubitril/valsartan treatment, the following investigations were performed as part of routine clinical care: echocardiography, bicycle exercise test with VO2max, a 6 min walking test (MWT), laboratory investigation including haemoglobin levels, kidney function, electrolytes and NT-pro-BNP and a quality of life (QOL) assessment. QOL was assessed with the Netherlands Organisation for applied scientific research/Academic Hospital Leiden adult Quality Of Life questionnaire (TAAQOL), which has been used previously to assess health-related QOL in adults with congenital heart disease.[20] It includes 45 questions and evaluates 12 different components of health-related QOL.

Figure 1 shows the treatment protocol. Depending on the previously used dose of ACEi or ARB, the starting dose of sacubitril/valsartan was chosen: if patients were using at least 80 mg of valsartan two times a day or an equivalent dose (perindopril 4 mg one time a day, lisinopril 20 mg one time a day, enalapril 20 mg one time a day, losartan 100 mg one time a day, irbesartan 300 mg one time a day, telmisartan 20 mg one time a day or candesartan 32 mg one time a day), the starting dose of sacubitril/valsartan was 49/51 mg two times a day. If the previous dose of ACEi/ARB was less than (the equivalent of) valsartan 80 mg two times a day, the starting dose of sacubitril/valsartan was 24/26 mg two times a day.[19] Patients were instructed to wait 36 hours after taking the last dose of ACEi prior to initiating treatment with sacubitril/valsartan to reduce the risk of angioedema.[11, 19]

After 2–4 weeks of treatment with the starting dose, blood pressure, weight, kidney function and complaints were evaluated. If the medication was well tolerated, the dose of sacubitril/valsartan was increased in a stepwise fashion until the highest tolerated dose was reached. Potassium increase to >5.5 mmol/L and/or an increase in creatinine >221µmol/L (or eGFR <30 mL/min/1.73m2) was followed by a step down in the dose and follow-up after 2–4 weeks. In the case of potassium increase >6 mmol/L and/or an increase in creatinine >310 µmol/L (or eGFR <20 mL/min/1.73 m2), the medication was stopped. Symptomatic hypotension and/or signs of decompensation were also followed by a stepdown or termination of treatment.

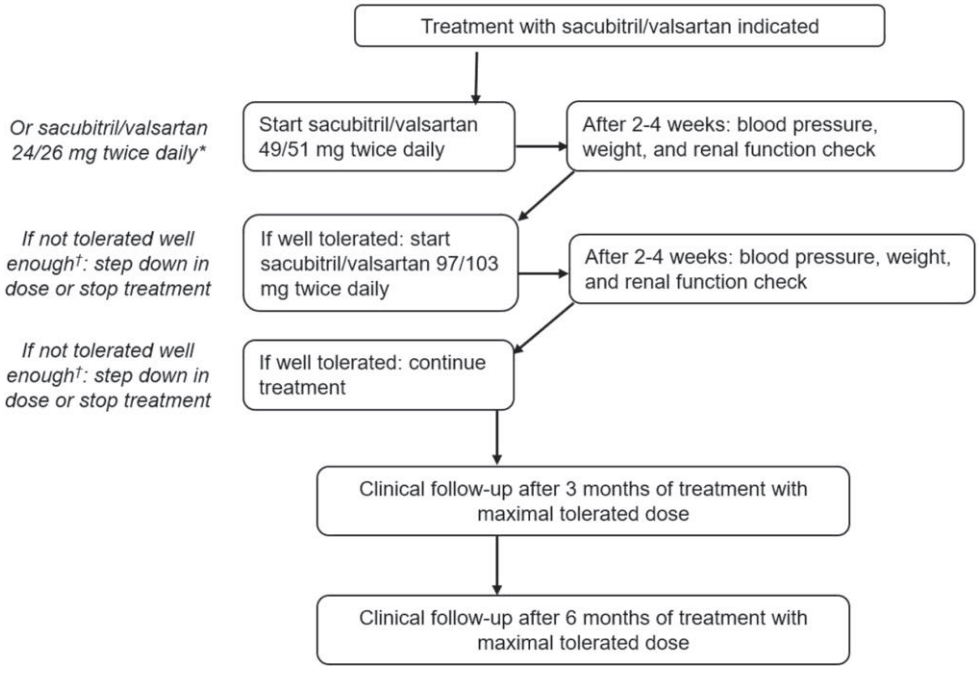

Figure 1: Treatment and follow-up protocol.
**Depending on previous dose of ACEi/ARB. †If potassium >5.5 mmol/L, increase in creatinine >310 µmol/L (or eGFR <20 mL/min/1.73 m2), hypotension or signs of decompensation. ACEi, ACE inhibitors; ARB, angiotensin II-receptor blockers.*

After 3 months of treatment with the optimal tolerated dose, blood pressure, weight, adverse events and laboratory investigations (including haemoglobin levels, kidney function, electrolytes and NT-pro-BNP) were repeated. After 6 months, echocardiography, bicycle exercise test with VO2max, a 6-MWT and laboratory investigations were re-evaluated, combined with physical examination and the TAAQOL questionnaire.

The serial echocardiograms were performed with commercially available ultrasound systems and were analysed offline in EchoPAC, GE Medical Systems. The echocardiographic parameters were assessed and measured offline by two cardiologists with expertise in congenital imaging blinded to the study (all echocardiograms were performed as standard of care and clinical follow-up at our centre).

Ethics statement

All tests and procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki declaration or comparable ethical standards. Appropriate local scientific board approval was obtained and the need for written informed consent was waived by the institutional medical ethical board. All patients provided consent for registration of their data and publication.

Patient and public involvement

Patients were informed about the research process and the background knowledge at initiation of treatment. The research questions and outcome measures were developed in consensus between the researchers and the treating cardiologists of this patient group (based on their extensive clinical experience). All the tests and procedures described were part of optimal patient care. The study results will be disseminated through national and local patient information websites.

Statistical analysis

All statistical analyses were performed in IBM SPSS V.23. Normally distributed continuous data are displayed as mean±SD and non-normally distributed continuous data are displayed as median (IQR). Proportions are displayed as numbers (percentages). For the comparison of values over time, paired samples t-tests or Wilcoxon rank tests were used as appropriate. A value of $p<0.05$ was considered to be statistically significant.

Results

Baseline clinical characteristics and sacubitril/valsartan initiation

Between January and August 2019, 20 consecutive patients with systemic RV failure who fulfilled the inclusion criteria initiated treatment with sacubitril/valsartan (*online supplemental Table 1*). Mean age was 46±11 years, and 50% were women. In one patient (patient 7), sacubitril/valsartan treatment was discontinued due to uncontrollable thirst with subsequent ample fluid intake and admission with cardiac decompensation. Another patient who was in end-stage heart failure at baseline (patient 8) declined screening for a VAD and died of progressive cardiogenic shock despite initiating treatment with sacubitril/valsartan. The 18 remaining patients were further analysed. Twelve patients (67%) had TGA corrected with the Mustard or Senning atrial switch procedure, and six patients (33%) had ccTGA.

The target dose of 97/103 mg sacubitril/valsartan two times a day was reached in 12 (67%) patients. Four patients (22%) had a maximum tolerated dose of 49/51 mg two times a day and two patients (11%) had a maximum tolerated dose of 24/26 mg two times a day. The reason to not further increase the dosage was symptomatic hypotension in all cases. None of the patients developed clinically relevant hyperkalaemia or significant deterioration of the renal function.

Follow-up after six months of treatment

Laboratory results

There was a significant decrease in NT-pro-BNP after 6 months of sacubitril/valsartan use (median 950–358 ng/L, p<0.001, *Table 1*). Relative reduction of NT-pro-BNP per patient is (percentage from baseline levels) shown in *Figure 2*. Overall, the median reduction in NT-pro-BNP was 45% (IQR 26–60) of the value at treatment initiation. In two patients (patient 15 and 19), there was an increase in NT-pro-BNP.

Table 1: Changes in the laboratory values 6 months after initiation of sacubitril/valsartan treatment, n=18

Laboratory values	Mean±SD or median (IQR) Baseline	Mean±SD or median (IQR) 6 months	P value
Hb (mmol/L)	8.7±0.9	8.9±0.9	0.08
Ht (L/L)	0.42±0.04	0.43±0.04	0.004*
MCV (fL)	89±5	91±3	0.006*
MCH (fmol)	1.84±0.12	1.86±0.07	0.251
RDW (%)	13.0±1.2	12.9±1.1	0.252
Sodium (mmol/L)	140±2	141±2	0.182
Potassium (mmol/L)	4.3±0.4	4.5±0.3	0.011*
Creatinine (µmol/L)	86±18	89±14	0.095
eGFR (mL/min/1.73 m2)	85±20	80±21	0.087
BUN (mmol/L)	6.5 (5.5–6.8)	6.3 (4.9–7.5)	0.649
ASAT (U/L)	31±13	29±13	0.162
ALAT (U/L)	30±11	26±12	0.013*
Gamma GT (U/L)	39 (26–82)	43 (27–62)	0.767
Total bilirubin (µmol/L)	11.5 (7.8–18.3)	10 (8.0–17.0)	0.550
CK (U/L)	93±40	105±58	0.328
Troponin T (ng/L)	11.0 (5.3–16.8)	7.5 (6.0–11.3)	0.109
NT-pro-BNP (ng/L)	950 (364–1235)	358 (233–639)	<0.001*

**Statistically significant. ALAT, alanine transaminase; ASAT, aspartase aminotransferase; BUN, blood urea nitrogen; Gamma GT, gamma glutamyltransferase; Hb, haemoglobin; Ht, haematocrit; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; NT-pro-BNP, N-terminal pro–B-type natriuretic peptide; RDW, red blood cell distribution width.*

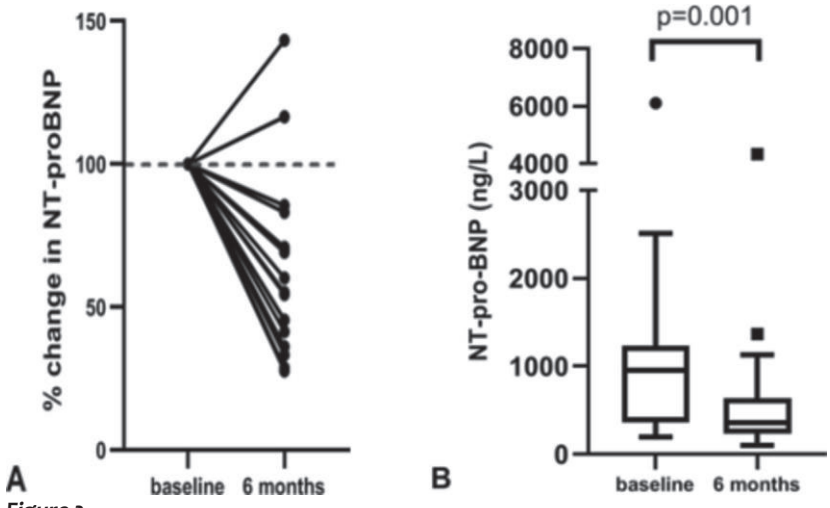

Figure 2

(A) Percentage of change in NT-pro-BNP at 6 months compared with the levels of individual patients at baseline. (B) Absolute NT-pro-BNP levels at baseline and 6 months, showing median (horizontal line) with IQR (box), lower and upper extreme (whiskers) and outliers (values represented with ● and ■). NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

There was a significant increase in both haematocrit and mean corpuscular volume (MCV), and a significant decrease in alanine transaminase (ALAT) levels. There was a statistically significant, but clinically irrelevant, increase in potassium and the eGFR did not change significantly (*Table 1*).

Echocardiography

There was an improvement in echocardiographic systemic RV function as accessed by the fractional area change ($p<0.001$) and in echocardiographic RV global longitudinal strain values ($p=0.014$) (*Table 2*). The global assessment of RV function using eye balling technique, the RV end diastolic diameter and severity of tricuspid regurgitation did not change significantly following 6 months of treatment. The function of the subpulmonary LV remained stable.

Table 2: Changes in physical examination, echocardiography and functional status 6 months after initiation of sacubitril/valsartan treatment, n=18

Variable	Mean±SD Baseline	Mean±SD 6 months	P value
General			
NYHA class (n, %)			0.112
II	13 (72%)	15 (83%)	
III-IV	5 (28%)	3 (17%)	
Systolic blood pressure (mm Hg)	106±10	106±14	0.960
Weight (kg)	80±18	79±18	0.187
6 min walking distance (m)	564±104	600±72	0.011*
Echocardiography			
Global RV function, (n, %)			0.157
Mildly reduced	4 (22%)	5 (28%)	
Moderately reduced	10 (56%)	10 (56%)	
TAPSE (mm)	12±2	11±2	0.211
RV FAC (%)	19±7	22±7	<0.001*
RV GLS (%)	−11±3	−13±2	0.014*
RVEDD (mm)	59±9	58±8	0.067
Tricuspid valve regurgitation (n, %)			1.000
Grade I–II	15 (88%)	15 (88%)	
Grade III–IV	2 (12%)	2 (12%)	
LV GLS (%)	−16±4	−18±5	0.110
MAPSE (mm)	18±5	18±3	0.663
Exercise testing			
Exercise capacity (W)	129±50	132±47	0.402
Exercise capacity (%)	79±17	81±17	0.575
VO2max (ml/min/kg)	18±5	18±4	0.886
% of predicted VO2max achieved	59±15	58±13	0.746
% of predicted heart rate achieved	77±13	78±14	0.717
Heart rate reserve (bpm)	66±24	65±26	0.795
RER	1.20±0.09	1.17±0.07	0.367

**Statistically significant. bpm, beats per minute; FAC, fractional area change; GLS, global longitudinal strain; LV, (subpulmonary) left ventricle; MAPSE, mitral annular plane systolic excursion; NYHA, New York Heart Association functional classification; RER, respiratory exchange ratio; RV, (systemic) right ventricle; RVEDD, (systemic) right ventricular end diastolic diameter (basal measurement); TAPSE, tricuspid annular plane systolic excursion.*

Clinical characteristics

The 6 min walking distance slightly increased from a mean of 564–600 m (p=0.011). The NYHA functional class, blood pressure, weight and maximal exercise capacity as assessed with exercise testing remained stable and none of the patients showed clinical deterioration during the study period (*Table* 2).

Quality of life

Sixteen patients completed the TAAQOL questionnaire at both time points (response rate 89%). The results are shown in *Table* 3. Higher scores (maximum 100) indicate higher QOL. After 6 months of treatment with sacubitril/valsartan, QOL regarding cognitive function, sleep and vitality domains improved significantly (p=0.015, p=0.007 and p=0.037, respectively, *Table* 3). In the other domains, there were no significant changes.

Table 3: Quality of life as assessed with the TAAQOL questionnaire, n=16

Scales	Mean±SD or median (IQR) Baseline	Mean±SD or median (IQR) 6 months	P value
Cognitive function	72 (38–98)	91 (70–100)	0.015*
Sleep	50 (38–86)	88 (36–100)	0.007*
Pain	75 (41–100)	78 (63–100)	0.152
Social functioning	97 (88–100)	100 (78–100)	1.000
Daily activities	72 (34–98)	84 (64–98)	0.395
Sexuality	100 (25–100)	100 (47–100)	0.344
Vitality	49±32	64±27	0.037*
Positive emotions	68±28	71±23	0.657
Depressive emotions	75±25	75±20	0.942
Aggressive emotions	100 (81–100)	100 (81–100)	0.673

Discussion

In this study, the tolerability and the effects of sacubitril/valsartan treatment in a single-centre cohort of adult patients with systemic RV failure were evaluated. Six months of treatment resulted in (1) a significant reduction in NT-pro-BNP levels (2) a subtle improvement in systemic RV function as assessed by echocardiography and (3) improvement in the 6 min walking distance and health-related QOL, without high rates of treatment discontinuation, symptomatic hypotension, hyperkalaemia or renal function decline.

This is the first cohort of patients with systemic RV heart failure treated with sacubitril/valsartan. As opposed to the recent work of Maurer et al, our findings show that this specific group of patients can indeed benefit from treatment with sacubitril/valsartan.[21] Previous studies with smaller cohorts or populations mixed with other types of congenital heart defects show neutral or tentatively positive results but do not perform formal statistics or do not concern patients with systemic RV specifically.[21 22] Our findings provide new insight into the pharmacological possibilities of heart failure treatment in the patients with systemic RV and justify assessment in larger prospective cohorts.

Secondary analysis of the cohort described in the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial showed a median decrease of NT-pro-BNP of 28% after the first 8–10 weeks of treatment.[16] Furthermore, the proportion of patients in which the treatment was limited by symptomatic hypotension, hyperkalaemia or a decline in renal function in the PARADIGM- HF trial was low.[11] In the current cohort, the median decrease in NT-pro-BNP was 45% after 6 months of treatment. There were no cases in which titration was halted or treatment had to be discontinued due to hyperkalaemia or decline in renal function, perhaps reflecting on the usually preserved subpulmonary function of the anatomic LV and preserved renal function. The observed rise of haematocrit, MCV and decrease in ALAT levels may be attributed to a net excretion of excess volume and subsequent relief of the hemodynamically congested liver. In a third of the patients, the maximum dose of 97/103 mg two times a day was not reached due to symptomatic hypotension, but lower doses were well tolerated. Similar proportions of patients reaching the maximum dose are described in other retrospective cohorts in patients with non-congenital heart disease and the maximally tolerated dose remains a matter of individualised patient care.[23]

Identification of patients in the early stages of deterioration of systemic RV function remains a challenge as patients with complex congenital heart disease are typically used to living with limitations in their exercise tolerance and detection of subtle changes using routine echocardiography is technically challenging. Despite this, finding the optimal window for optimisation of medical therapy to stimulate reverse myocardial remodelling and improve the long-term outcome is crucial. BNP and NT-pro-BNP levels may provide a useful clinical tool in identifying and managing adult patients with congenital heart disease.[24] The correlation of NT-pro-BNP and clinical and echocardiographic parameters in our study is illustrative of this. A recent study evaluating medication use in adults after atrial switch for TGA showed that only the symptomatic patients with systemic RV benefited from the use of heart failure medication, suggesting that adequate patient selection is key and discouraging prophylactic use of heart failure medication in this patient group.[25]

A recent study of sacubitril/valsartan in an animal model of RV pressure overload showed that sacubitril/valsartan prevented maladaptive RV remodelling by diminishing the effective RV pressure increase, hypertrophy, collagen and myofibre reorientation and amelioration of tissue stiffening. This provides some insight into the potential mechanism of action of sacubitril/valsartan in the failing (systemic) RV.[26]

Of interest is the discrepancy between the only slightly reduced distance attained during the 6-MWT (564 m), which improved after 6 months of treatment with sacubitril/valsartan and the unaffected, poor performance as assessed by exercise testing and VO2max (VO2max 18 mL/min/kg, 59% of predicted) in our study population. Patients with preserved systemic RV function are known to have significantly lower peak and anaerobic threshold oxygen uptake compared with age matched controls. In addition, impaired systemic RV function further reduces the peak oxygen uptake.[27] Perhaps the limited contractile reserve and poor tolerance of pressure overload of the systemic RV can explain the poor performance during peak exercise training such as seen during the exercise testing. Although the 6-MWT is best reflective of low intensity exercise capacity, most daily activities are of low intensity and therefor the observed improvement in 6-MWT performance is promising.

As compared with the general population, adults with congenital heart disease have a worse self-perceived health-related QOL. This may be even worse in patients with complex congenital defects.20 Secondary analysis of the PARADIGM-HF trial showed improvement in QOL in both physical and mental domains.[28] In the current cohort, improvements were seen in the domains of cognitive function, sleep and vitality after 6 months of treatment with sacubitril/valsartan, suggesting that, although this was an

open-label study, the self-perceived QOL can indeed be improved with medical intervention.

Study limitations

This study is limited by its single-arm, non-blinded design and the relatively small study population, reflective of the rarity of the condition. The findings should be interpreted taking into account the open-label nature of the study. Therefore, the results should be confirmed in a larger, preferably randomised, double-blinded and placebo-controlled trial.

Conclusion

This is the first cohort of patients with systemic RV heart failure treated with sacubitril/valsartan. This appears to be well tolerated and leads to improvements in NT-pro-BNP and echocardiographic function. The positive results show the potential of sacubitril/valsartan in the treatment of this patient population.

Clinical perspectives

With the current survival rates of 82% at 40 years after atrial switch operation for TGA and 84% survival at the age of 40 in patients with ccTGA, the burden of systemic RV heart failure in this young population will increase over the next decades.[29] Heart failure treatment in this patient group remains a challenge. Optimisation of pharmacological treatment, aggressive treatment of arrhythmias, the search of adequate pacing modalities including resynchronisation therapy and timely surgical treatment of TR all play an important role in halting the progression of systemic RV heart failure. The specific anatomical and physiological characteristics, together with extensive surgical history and scarce numbers of donor hearts often makes this group unsuitable for cardiac transplantation. When confronted with advanced heart failure, VAD implantation as destination therapy shows promising results in patient with systemic RV failure.[30] The present study demonstrates that sacubitril/valsartan results in improved RV function, exercise capacity and QOL in symptomatic patients with systemic RV.

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Chapter 8

Potential of eHealth smart technology in optimization and monitoring of heart failure treatment in adults with systemic right ventricular failure

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Abstract

Aims

Patients with a systemic right ventricle (sRV) in the context of transposition of the great arteries (TGA) after atrial switch or congenitally corrected TGA are prone to heart failure and arrhythmias. This study evaluated feasibility, patient adherence, and satisfaction of a smart technology-based care pathway for heart failure treatment optimization in these patients.

Methods and results

Patients with symptomatic sRV failure eligible for initiation of sacubitril/valsartan were provided with four smartphone compatible devices (blood pressure monitor, weight scale, step counter, and rhythm monitor) and were managed according to a smart technology-based care pathway. Biweekly sacubitril/valsartan titration visits were replaced by electronical visits, patients were advised to continue measurements at least weekly after titration. Data of 24 consecutive sRV patients (median age 47 years, 50% female) who participated in the smart technology-based care pathway were analysed. Median home-hospital distance was 65 km (maximum 227 km). Most patients (20, 83.3%) submitted weekly measurements; 100% submitted prior to electronical visits. Titration conventionally occurs during a hospital visit. By implementing eHealth smart technology, 68 such trips to hospital were replaced by virtual visits facilitated by remote monitoring. An eHealth questionnaire was completed by 22 patients (92%), and 96% expressed satisfaction. After titration, 30 instances of remote adjustment of heart failure medication in addition to scheduled outpatient clinic visits occurred, one (4%) heart failure admission followed, despite ambulant adjustments. Five patients (21%) sent in rhythm registrations (n = 17), of these 77% showed sinus rhythm, whereas supraventricular tachycardia was detected in the remaining four registrations.

Conclusion

These data suggest that implementation of a smart technology-based care pathway for optimization of medical treatment sRV failure is feasible with high measurement adherence and patient satisfaction.

Introduction

The number of patients with congenital heart disease (CHD) is growing, with currently over 90% survival to adulthood. Despite the improved surgical outcomes, these patients remain at risk for long-term complications such as heart failure, arrhythmias, and pulmonary hypertension and require lifelong follow-up.[1] In the 21st century, there has been a significant rise in the development and implementation of telemonitoring with smart technology devices and eHealth. The use of telemonitoring via smart technology has shown conflicting results in patients with acquired heart disease, especially in terms of reducing mortality and hospitalizations,[2–5] yet studies in adult CHD have been carefully optimistic.[6–10]

The adult CHD population seems particularly eligible for smart technology since they are generally younger than the average cardiac patient, are more likely to be in the possession of a smartphone device, and have a high degree of digital literacy.[9] Previous studies have also shown that they are highly motivated for telemonitoring and eHealth.[9,11] Care for these patients requires a high degree of specialization and structural follow-up in an expertise centre is indicated for patients with heart failure in the context of CHD.[1] The concentration of care in these tertiary centres often leads to longer travel time and interference with daily (work-) obligations for patients. In addition, patients with CHD have shown to have high utilization of emergency care resources.[1] These factors could make this population particularly fit for telemonitoring via smart technology.[9–11]

Patients with a systemic right ventricle (sRV)—a morphological right ventricle in a subaortic position supporting the systemic circulation—in the context of transposition of the great arteries (TGA) after atrial switch or congenitally corrected TGA are particularly prone to long-term complications, including sRV heart failure and arrhythmias.[1,12–15] Although there are no specific recommendations in the current guidelines for the use of heart failure medication in this population, it is carefully and pragmatically prescribed in sRV failure based on expert opinion, small trials, and lack of alternatives.[1] A recent analysis of 150 adult atrial switch patients in the Netherlands showed decreased mortality in symptomatic patients treated with renin–angiotensin–aldosterone system (RAAS) inhibitors and β-blockers[16] and beneficial effects of sacubitril/valsartan treatment in adults with sRV failure on N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and echocardiographic function have recently been reported.[17] The aim of the current study was to evaluate the feasibility, patient adherence, and appreciation of a smart technology-based care pathway for heart failure treatment optimization and monitoring in sRV failure. The secondary outcome

of this study was to evaluate the potential of the smart technology-based care in detection of arrhythmias in this group.

Methods

Design and inclusion/exclusion criteria

In this single-centre, non-blinded cohort study performed at the Department of Cardiology at the Leiden University Medical Center, data on all adult patients with a failing sRV in a biventricular circulation who were started on sacubitril/valsartan according to the smart technology-based care pathway in February 2019—February 2020, were reported. Patients who had an (estimated) sRV ejection fraction of ≤40% and had persisting symptomatic heart failure (NYHA class ≥ II) despite treatment with highest tolerated doses of a β-blocker and/or an angiotensin-converting enzyme inhibitor/angiotensin II receptor-blocker for a period of at least 3 months were advised to start treatment with sacubitril/valsartan.[17] Patients who were started on sacubitril/valsartan (n = 25) were offered four smartphone compatible devices (blood pressure monitor, weight scale, step counter, and rhythm monitor). If they accepted (n = 24), they were treated and monitored according to a smart technology-based care pathway (*Figure 1*). One patient declined participation in digital monitoring due to personal preference for face-to-face meetings with the cardiologist in the outpatient clinic. The conventional pathway consisted of a biweekly visit to the outpatient clinic with either the treating cardiologist or physician assistant specialized in heart failure. Check-up consisted of assessment of complaints, physical examination including blood pressure and weight monitoring and laboratory workup. The smart technology-based pathway was designed based on the previously validated care pathway in post-myocardial infraction patients and consisted of measurements performed by the patients twice a week with the blood pressure monitor and weight scale and biweekly (every 2nd week) consultations by telephone, including assessment of complaints, smart technology measurements, and laboratory workup.[18] Patients were instructed to perform laboratory workup at their general practitioner and to perform the above measurements and a single-lead electrocardiogram (ECG) registration in case of complaints of palpitations (*Figure 1*). Patients were stimulated to use the step counter daily.

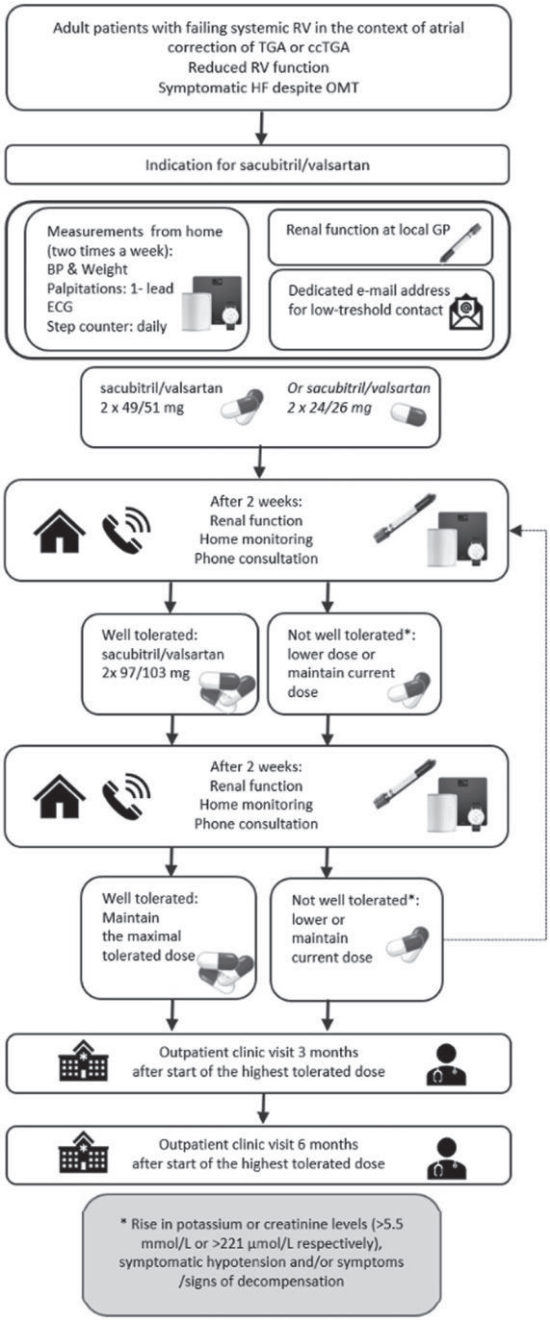

Figure 1: Sacubitril/valsartan titration according to the smart technology care pathway.

BP, blood pressure; ccTGA, congenitally corrected transposition of the great arteries;

GP, general practitioner; HF, heart failure; OMT, optimal medical treatment; RV, right ventricle; TGA, transposition of the great arteries.

Materials

The blood pressure monitor (Connect, Wi-Fi Smart Blood Pressure Monitor), step counter (Move, activity and sleep watch), and weight scale (Body, Weight and BMI Wi-Fi Scale) were from the brand Withings and compatible with the Health Mate app for iOS and Android. The blood pressure monitor is an oscillometric device, not requiring assistance from health-care personnel. The rhythm monitor used was from Alivecor KardiaMobile (mobile single-lead ECG) and was compatible with the Kardia app for iOS and Android (*Figure* 2). The rhythm monitor generates a single-lead ECG rhythm strip after manual initiation by the patient. All devices used have European Conformity (CE) marking and have been previously clinically validated and/or tested.[19–21] A dedicated eHealth team instructed and assisted patients during installation and use of these devices and the corresponding apps. A dedicated email address and telephone number were available for 'on demand' assistance.

Figure 2 eHealth devices, including weight scale, blood pressure monitor, step counter, and rhythm monitor

(A) Blood pressure monitor (Withings Wi-Fi Smart Blood Pressure Monitor); (B) weight scale (Withings Body, Weight and BMI Wi-Fi Scale); (C) step counter (Withings Move, activity and sleep watch); and (D) rhythm monitor (Alivecor KardiaMobile).

Treatment and follow-up

The smart technology-based care pathway is summarized in *Figure 1*. A dedicated email address was made available for low threshold contact for patients during the titration process and follow-up.

After 2 weeks of treatment with the starting dose or after dosage modification, blood pressure, weight, complaints, and laboratory findings (renal function, potassium level) were evaluated in a telephone consultation. Data from telemonitoring devices and laboratory values (blood samples drawn at the local general practitioner's office) were collected from the hospitals patient information systems (EPD-Vision, Leiden, the Netherlands and Hix, Chipsoft, Amsterdam, the Netherlands). If the medication was well tolerated, the dose of sacubitril/valsartan was increased in a stepwise fashion according to clinical protocol. These steps were repeated until the highest tolerated dose or maximal dose of 97/103 mg was reached. Rise in potassium or creatinine levels (>5.5 mmol/L or >221 µmol/L, respectively), symptomatic hypotension, and/or symptoms or signs of decompensation (e.g. weight gain) were followed by a step-down or termination of treatment.

After 3 and 6 months of treatment with the optimal tolerated dose, blood pressure, weight, symptoms, and laboratory investigations (including haemoglobin levels, kidney function, electrolytes, and NT-pro-BNP) were repeated, followed by a consultation in the hospital.

Outcomes

Feasibility (technical and practical consideration of the pathway making it fit for implementation in daily clinical practice), potential to reduce physical hospital visits, patient adherence and satisfaction, and detection of arrhythmias were measured and evaluated by manual assessment of patient information and a questionnaire.

Patient information was derived through assessment of the electronic patient information systems, distance from home to hospital was assessed using the quickest route as indicated in Google Maps route planning. Minimal one-way travel time was assessed using the quickest travel time by car without traffic in Google Maps. Patients were instructed to measure weight and blood pressure twice a week and were stimulated to wear the step counter daily. Patients were instructed to make a single-lead ECG registration if they experienced palpitations or other rhythm-related symptoms. Data were automatically and safely imported into the electronic patient health record file and were only accessible to the medical team. The single-lead ECGs

were evaluated by the treating cardiologist and followed-up with a telephone or email contact. Patients were instructed to continue measurements once to twice a week.

Patient satisfaction was assessed by an anonymous questionnaire. Patients were asked to evaluate the use of smart technology in the process of titration of new heart failure medication 3 months after optimal dose. This was done by a self-developed dedicated questionnaire (*Supplementary material online*) consisting of 19 questions and evaluates feasibility, user satisfaction, usability, and overall rating. The results were anonymized and analysed by the study investigators. The treating physician did not have access to the results of the questionnaire during the study period.

Ethics statement

All tests and procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 2013 Helsinki declaration or comparable ethical standards and according to Dutch legislation for handling of personal data.

Consent

Appropriate local scientific board approval was obtained and the need for written informed consent was waived by the institutional medical ethical board. All patients provided consent for registration of their data and publication.

Statistical analysis

All statistical analyses were performed in IBM SPSS version 25. Normally distributed continuous data are displayed as mean ± standard deviation and non-normally distributed continuous data are displayed as median [quartile 1, quartile 3]. Proportions are displayed as numbers (percentages).

Results

Patient characteristics

In total, 24 sRV patients (median age 47 years, 50.0% female) were included in the analysis of the primary outcome (*Table 1*). Median follow-up time was 17 months [14; 19]. Sixteen patients (66.7%) had TGA corrected with the Mustard or Senning atrial switch procedure, and eight patients (33.3%) had ccTGA. 87.5% had a moderately to severely reduced sRV function. The NYHA functional class was II in 17 patients (70.8%) and class III–IV in 29.2%. The median home-hospital distance was 65 km [28; 121], with a maximal distance of 227 km. Median minimal travel time (one-way trip) was 52 min [29; 93], with a maximal time of 158 min.

Table 1: Patient characteristics at baseline (n = 24)

Patient characteristics	Baseline (n = 24)
Age (years) (median [Q1; Q3])	47 [44; 50]
Female (n, %)	12 (50.0%)
Anatomy (n, %)	
TGA with atrial switch procedure	16 (66.7%)
ccTGA	8 (33.3%)
sRV function (n, %)	
Mildly reduced	3 (12.5%)
Moderately reduced	16 (66.7%)
Severely reduced	5 (20.8%)
Tricuspid regurgitation (n, %)	
Grade I	11 (45.8%)
Grade II	12 (50.0%)
Grade III	0 (0%)
Grade IV	1 (4.2%)
NYHA (n, %)	
NYHA II	17 (70.8%)
NYHA III–IV	7 (29.2%)
History of SVT (n, %)	14 (58.3%)
Atrial fibrillation	9 (37.5%)
Atrial flutter	8 (33.3%)
Atrial tachycardia	10 (41.7%)
AVNRT	4 (16.7%)
SVT ablation (n, %)	10 (41.7%)
Pacemaker/ICD (n, %)	13 (54.2%)
Distance to hospital (km) (median [Q1; Q3])	65 [28; 121]

AVNRT, atrioventricular nodal re-entrant tachycardia; ccTGA, congenital corrected transposition of the great arteries; ICD, Implantable cardioverter-defibrillator; NYHA, New York Heart Association Functional Classification; Q1, quartile 1; Q3, quartile 3; sRV, systemic right ventricle; SVT, supraventricular tachycardia; TGA, transposition of the great arteries.

Titration process and feasibility

Of all 24 patients, 12 (50.0%) had two contact moments for the titration of the medication before the final dose was achieved. In the other patients, a maximum of five contact moments was required to titrate to the maximum tolerated dose. This saved a total of 68 trips to the hospital compared with the conventional outpatient clinic titration process. Thirteen patients (54.1%) could be titrated to the maximal dose of sacubitril/valsartan (97/103 mg). No episodes of hyperkalaemia or deterioration of renal function were observed. One patient (4.2%) discontinued sacubitril/valsartan treatment 2 months after initiation. Other patients (n = 10, 41.7%) did not reach the maximal dose due to (symptomatic) hypotension.

Patient adherence and experience

Of 24 patients, 83.3% of patients submitted measurements twice a week during the titration process. All patients (100%) submitted measurements prior to visits as requested. After titration, 50.0% continued weekly measurements and 70.8% continued (at least) monthly measurements. Twelve patients (50.0%) wore the step counter daily. On average, patients took 429 ± 1976 steps a day. Twenty-two patients completed the eHealth questionnaire (response rate 91.7%, *Figures* 3 and 4).

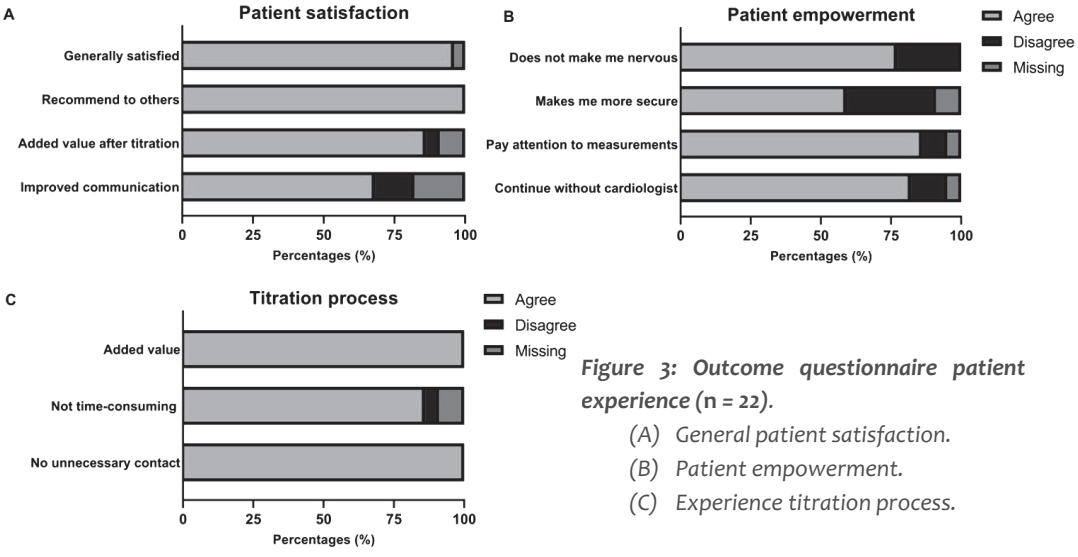

Figure 3: Outcome questionnaire patient experience **(n = 22).**

(A) General patient satisfaction.

(B) Patient empowerment.

(C) Experience titration process.

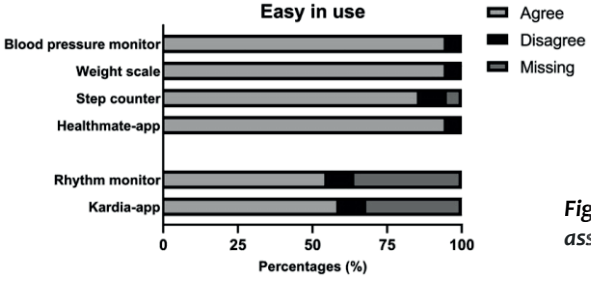

Figure 4: ***Outcome questionnaire assessment of usability*** **(n = 22).**

Patient satisfaction

Twenty-one patients (95.5%) expressed satisfaction with the smart technology intervention. All patients would recommend the smart technology intervention to others. Nineteen patients (86.4%) considered the smart technology intervention to be of a continued added value after titration and 15 (68.2%) thought it improved their communication with the cardiologist (*Figure 3A*).

Patient empowerment

The smart technology intervention made 59.1% (n = 13) of the patients feel more secure and 22.7% (n = 5) of the patients more nervous. Nineteen patients (86.4%) looked at and paid attention to their own measurements and 18 (81.8%) would continue even if the cardiologist would not look at the measurements (*Figure 3B*).

Titration process

All patients considered the smart technology intervention of value during the titration process, most (86.4%, n = 19) did not think it was too time-consuming. None of the patients thought the cardiologist reached out to them unnecessarily because of the measurements (*Figure 3C*). Fourteen patients (63.6%) found this the best way for the titration of medication, while four patients would have preferred a different way of titration. Two patients (8.3%) would have preferred titration through physical outpatient visits, one (4.2%) patient would have preferred titration through the general practitioner's office, and one other (4.2%) would have preferred a combination of both smart technology and physical visits.

Usability

Twenty-one (95.5%) patients thought that the blood pressure monitor, scale, and Healthmate App were easy to use and 86.4% considered the step counter to be easy in use. The rhythm monitor and Kardia App was considered easy to use by 54.5% (36.4% missing), and 59.1% (31.8% missing), respectively (*Figure 4*).

Heart failure

After the titration to the highest tolerated dose, there was a total of 30 contact moments by telephone or email in six patients (25%) in response to home measurements and symptoms, resulting in adjustment of heart failure medication.

One patient discontinued treatment of sacubitril/valsartan and measurements through telemonitoring after a heart failure-related admission. Despite the patient having sent in measurements and repeated contact moments with the treatment team due to congestion-related symptoms and subsequent ambulant medication adjustments,

heart failure-related admission was not prevented. (n = 1, 4.2%). No other heart failure-related admissions were observed during the study period.

Detection of arrhythmia

A total of 14 patients (58.3%) had a history of supraventricular arrhythmia's, 12 patients experienced more than one arrhythmia. Nine patients (37.5%) had a history of atrial fibrillation, 8 (33.3%) of atrial flutter, 10 (41.7%) of atrial tachycardia, and 4 (16.7%) of atrioventricular (AV) nodal re-entry tachycardia. In total, 10 patients (41.7%) had undergone at least one ablation procedure of a supraventricular arrhythmia prior to the study period.

Five patients (20.8%) sent in a single-lead ECG registration using the provided smart technology rhythm monitor (*Figure* 5). One patient sent in an ECG due to chest discomfort, all other registrations were made due to palpitations. All patients who sent in an ECG due to palpitation symptoms had a history of supraventricular arrhythmias. Of the 17 single-lead ECG registrations made during complaints, 13 (76.5%) showed sinus rhythm, consequently reassuring the patients and potentially saving a trip to the emergency department or general practitioner's office. Four registrations (23.5%) showed a supraventricular arrhythmia, of which one was an atrial flutter with alternating conductivity, and the three other ones were atrial tachycardias. These registrations resulted in three admissions for electrical cardioversion, one patient was already listed for electrophysiological study and ablation and decided not to present to healthcare services awaiting the already planned procedure. Classification of the exact type of supraventricular arrhythmia was done at admission based on a 12-lead ECG. Although the single-lead ECG registration provides information on the frequency and regularity and can help differentiate between supra- and ventricular origin of an arrhythmia, it has not been validated to diagnose the exact type of arrhythmia in a patient group with complex anatomy and intrathoracic cardiac position. No cases of novel arrhythmias were diagnosed through the smart technology rhythm monitor.

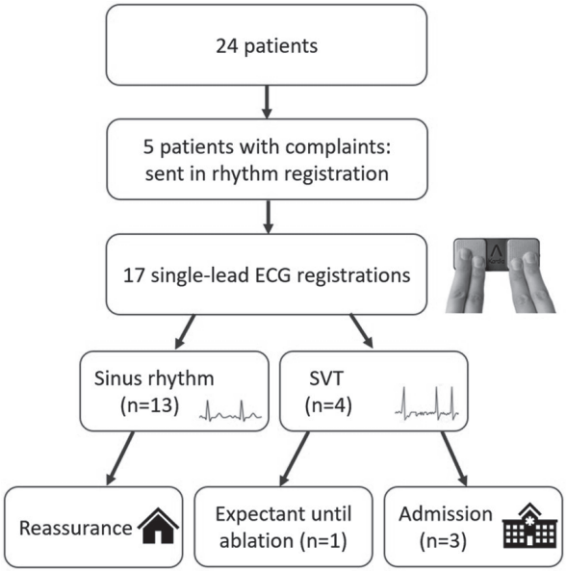

Figure 5: Detection of arrhythmia during 6 months of follow-up. *ECG, electrocardiogram; SVT, supraventricular tachycardia.*

Discussion

This is, to the best of our knowledge, the first study assessing feasibility of telemonitoring and titration of heart failure medication in adult patients with a failing systemic right ventricle in a biventricular circulation. The main findings of this study are1 eHealth can be effectively implemented as a part of a clinical care pathway to support medication optimization and titration in this patient group[2]; patient adherence and satisfaction is high; and[3] eHealth can be of potential value in the assessment of arrhythmias and avoiding unnecessary utilization of (emergency) health-care resources in this patient group.

Current results in light of previous studies

A review by Treskes et al.[9,22] showed that studies on telemedicine solutions for medication adherence are conflicting in the general population, yet a recent pilot showed that symptomatic CHD patients are suitable and highly motivated for eHealth implementation. Kauw and colleagues also reported promising results of eHealth used for telemonitoring in the CHD population.[6,10] Although several randomized controlled trials in acquired heart failure showed no benefit of eHealth in comparison to regular healthcare or treatment, eHealth was found feasible with a positive tendency to reduce readmissions and contacts with the treatment team.[3,5,23] Prospective studies on the use of eHealth and telemonitoring in CHD patients reported high adherence rates (97% and >70%, respectively) and patient satisfaction (84%), comparable to the results in the current patient group.[7,8] This can be explained by the high digital literacy of relatively

young adult CHD patients.[9] The results of this study therefore corroborate findings of previous studies regarding feasibility of eHealth in adult CHD (ACHD) patients. Based on the literature and the results of this study, specific patient eligibility characteristics for effective remote monitoring can be defined (*Table 2*). To avoid 'data overload',[24] we suggest that eHealth is used with an approach integrated into a care pathway tailored to specific predefined ACHD patient groups.

Table 2: Patient eligibility characteristics for complete remote monitoring

Patients who can be managed remotely	Patients who require hospital visits
Language proficiency in Dutch/English	Not fulfilling any of the criteria listed in the left column
Digital literacy	Episodes of congestion during titration process that require hospitalization
Adequate Wifi connection	(Near-) syncopal arrhythmia
Possession of a smart phone device	
Commitment and personal motivation to perform structural measurements in a timely manner	
No episodes of congestion/ deterioration of heart failure that would require hospitalization	

Optimization of medication

Titration of medication in sRV patient population can be challenging due to relatively low baseline blood pressures and poorly understood mechanism of action of heart failure medication in this group, combined with a busy lifestyle with work and personal commitments of these often relatively young patients, and long travel distance to expert clinical centres. By means of structural monitoring of the telemonitoring data and a dedicated email address for low threshold contact, it was possible to rapidly and accurately adjust heart failure medication during titration and follow-up. Several studies and case series on the effects of sacubitril/valsartan in ACHD patients are published to date.[17,25–27] Although sacubitril/valsartan was generally well tolerated, Maurer *et al.* did see a reduction in systolic and diastolic blood pressure and a deterioration of renal function, suggesting close monitoring during titration is essential. Our results suggest that eHealth guided titration process is feasible and is of additional value in this young patient group, saving 68 potential outpatient clinic visits.

This way of titration was also positively valued by the patients, as 63.6% found this to be the best way for titration. It also allowed for swift therapy changes to be made as a result of telemonitoring measurements in a substantial number of patients (25%).

Arrhythmia detection

Patients with an sRV in a biventricular circulation are prone to arrhythmias[1] which are a substantial cause of emergency department presentations and morbidity in this patient group.[11,28] We report a high prevalence of atrial arrhythmias in our study population (58.3%). The failing sRV is prone to further deterioration during atrial tachycardia and arrhythmias are a potential cause of sudden cardiac death in these patients.[1,29,30] This makes early detection and aggressive treatment of these arrhythmias of great importance. In our population, 10 out of 14 patients with known supraventricular arrhythmias had a history of ablation procedures. Telemonitoring has previously been shown to successfully detect supraventricular arrhythmias, and atrial fibrillation in particular.[31] Our data furthermore show that rhythm registrations obtained through the smart technology care pathway were predominantly normal sinus rhythm registrations, showing no arrhythmia (76.5%). These data are in line with previous work of Kauw *et al.*,[7] who reported 55% of rhythm registrations performed by 80 CHD patients to show sinus rhythm. This reflects on the high patient awareness of potential tachyarrhythmias and the ability of this technology to create remote patient assurance, self-management, and empowerment, and prevention of unnecessary emergency health-care utilization.

COVID-19 pandemic

Although the COVID-19 pandemic was beyond the scope of this study, it clearly demonstrated the need of non-contact care delivery and self- and telemonitoring of symptomatic patients.[32] Especially, in this vulnerable patient population, it is absolutely necessary to curtail hospital visits to avoid potential infections. Due to the COVID-19 pandemic, telemonitoring through smart technology has been rapidly and widely implemented as the 'new healthcare standard' allowing for the provision of the right care for the right patient at the right place. This study illustrates that if embedded in a regulated care pathway, eHealth can play an important role in care for ACHD patients in the 21st century.

Study limitations

This study is limited by its single-arm, non-blinded design, and the small study population. Although this is reflective of the rarity of the condition and the inability to blind patients for performing eHealth measurements, the findings reported should be interpreted taking into account the open nature of the study. Another limitation is the

lack of internationally validated questionnaires to assess patient satisfaction of eHealth. Ideally, results should be confirmed in a larger, randomized multicentre trial setting.

Conclusion

These data suggest that implementation of a smart technology-based care pathway for optimization of medical treatment for sRV failure is feasible with high measurement adherence and patient satisfaction. If implemented as a part of a regulated care pathway, eHealth has potential in improving healthcare and patient empowerment in the field of ACHD.

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Chapter 9

Ventricular assist device implantation in patients with a failing systemic right ventricle: a call to expand current practice

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Abstract

Ventricular assist device (VAD) implantation is an established treatment modality for patients with end-stage heart failure, and improves symptoms and survival. In the Netherlands, it is not yet routinely considered in patients with congenital heart disease and failing systemic right ventricle (SRV). Recently, a VAD was implanted in 2 SRV patients, one who underwent a Mustard procedure during infancy for transposition of the great arteries (male, 47 years old) and one with a congenitally corrected transposition of the great arteries (male, 54 years old). The first patient is doing well >1 year after implantation; the second patient will be discharged home soon. These examples and other reports demonstrate the feasibility of adopting VAD implantation into routine care for SRV failure. In conclusion, patients with SRV failure may be suitable candidates for VAD implantation: they are relatively young, usually have a preserved subpulmonary left ventricular function, and their specific anatomical and physiological characteristics often make them unsuitable for cardiac transplantation. Therefore it is important to recognise the possibility of VAD implantation early in the process of SRV failure, and to timely refer these patients to a heart failure clinic with experience in VAD implantation in this group of patients for optimisation, screening, and implantation.

Current use of ventricular assist device therapy and gap for patients with failing systemic right ventricle

Left ventricular assist device (LVAD) implantation as destination therapy is an established treatment for patients with end-stage heart failure who are not eligible for cardiac transplantation. It improves both symptoms and prognosis [1]. However, in the Netherlands, it has until recently not been used as a treatment option for congenital heart disease (CHD) patients with failing systemic right ventricle (SRV). This group includes patients late after Mustard or Senning procedure for transposition of the great arteries (TGA) or patients with congenitally corrected TGA (ccTGA). Current survival of Mustard/Senning patients is 82% at 40 years postoperatively [2]. For ccTGA patients, freedom from death or cardiac transplantation was 84% at 40 years of follow-up [3]. SRV failure is likely to be a major and substantial problem in the upcoming years [2, 3]; in our centre alone, 61 SRV patients are currently under follow-up. SRV patients have a complex anatomy, adhesions due to (sometimes multiple) prior sternotomies, and pulmonary hypertension, and are consequently likely to be rejected for cardiac transplantation due to current shortage of donor organs. The European Society of Cardiology (ESC) guideline for adult CHD does not yet contain an advice regarding VAD implantation but mentions long-term mechanical circulatory support as an important area of research [4]. Recently, we implanted a VAD in 2 SRV patients. In this paper we aim to illustrate the feasibility of this procedure, to stress the clinical necessity to expand current indications for VAD therapy to this group, and especially to consider it as destination therapy.

Cases of VAD implantation in SRV: clinical and surgical considerations

The first patient is a 47-year-old man late after Mustard procedure for TGA. The tricuspid valve (systemic atrioventricular valve) was replaced two years before VAD implantation because of severe regurgitation. After tricuspid valve surgery he developed symptoms of advanced heart failure (New York Heart Association [NYHA] class IIIb) despite optimal medical therapy. He was screened for cardiac transplantation and rejected due to pulmonary hypertension (mean pulmonary artery pressure 29.7 mm Hg, transpulmonary gradient 12.7 mm Hg, estimated pulmonary vascular resistance 4.2 Woods Units). SRV function was poor (2D global longitudinal strain [GLS] −4.7%, fractional area change [FAC] 9.2%). The subpulmonary left ventricular function was reasonable. The patient showed advanced symptoms of heart failure and, consequently, was screened and accepted for VAD implantation. Pre-operatively, the patient was optimised with inotropic support and was in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) level 3 at the time of surgery.

Through median re-sternotomy and with cardiopulmonary bypass, a VAD (HVAD, Medtronic, USA) was implanted in the SRV after resection of multiple trabeculations in the SRV cavum. Because of anatomical considerations, the VAD was positioned mid-basally instead of apically, which is common for VAD implantation in the left ventricle (*Figs. 1 and 2*). Postoperative transoesophageal echocardiography (TEE) demonstrated normal VAD inflow and outflow signals and good VAD performance. Recovery was uneventful for 13 days. Then, a re-operation was necessary because of cardiac tamponade; following re-operation patient recovered well. Shortly after discharge, the patient suffered a haemodynamically tolerated sustained monomorphic ventricular tachycardia (185/min), probably originating from the surgical scar, which was terminated with procainamide. Eight months postoperatively, an ischaemic stroke occurred under clopidogrel and an adequate international normalized ratio (INR), with mild cognitive sequelae. A risk factor in this may have been the aortic valve, which showed reduced opening after VAD implantation. His target INR was raised. His maximum workload (measured with bicycle ergometry) is still improving from 70 Watts pre-implantation, to 80 Watts after 6 months of VAD support, and to 90 Watts currently. More than 1 year postoperatively, the patient is doing well and functioning in NYHA class II.

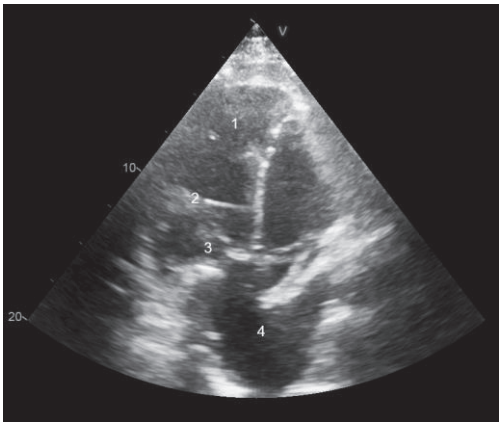

Figure 1: Transthoracic echocardiography of patient 1 after VAD implantation
1 systemic right ventricle 2 inflow cannula 3 tricuspid valve prosthesis 4 pulmonary venous tunnel

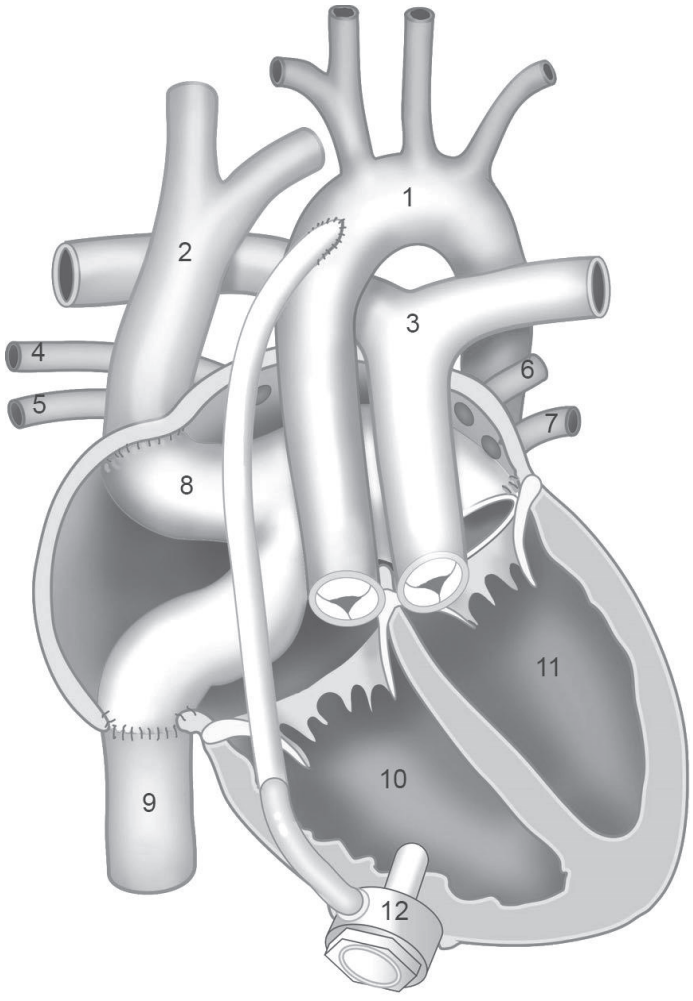

Figure 2: Anatomy of patient 1 after VAD implantation

1 aorta 2 vena cava superior 3 pulmonary trunk 4 right superior pulmonary vein 5 right inferior pulmonary vein 6 left superior pulmonary vein 7 left inferior pulmonary vein 8 baffle 9 vena cava inferior 10 systemic right ventricle 11 subpulmonary left ventricle 12 ventricular assist device

The second patient is a 54-year-old man with ccTGA, who underwent tricuspid valve replacement with a bioprosthesis and mitral valve annuloplasty 2 years before VAD implantation, the latter of which was complicated by partial ring dehiscence. The defect was closed percutaneously with 2 vascular plugs. In 2017, he received an ICD for primary prevention because of a poor SRV function. Recently, his clinical condition deteriorated rapidly and he was admitted because of congestion. He was rejected for cardiac transplantation because of renal dysfunction and, consequently, screened and accepted for VAD implantation. Transthoracic echocardiography (TTE) confirmed the poor SRV function (GLS –2.0%, FAC 7.3%). Pre-operative admission was prolonged due to biliary pancreatitis, which was treated with laparoscopic cholecystectomy. At the time of surgery, the patient was in NYHA class IV, INTERMACS level 2. Because of a decline in subpulmonary left ventricular function, treatment with levosimendan (Orion Corporation) was initiated. The VAD was implanted through a left-sided anterolateral thoracotomy combined with upper hemisternotomy because of a relatively dorsolateral position of the SRV and favourable anatomy for this approach. Again, multiple trabeculations were resected in the SRV cavum before the VAD (HVAD, Medtronic, USA) was implanted. Early after surgery, VAD flow dropped due to a deviation of the inflow cannula towards the septum resulting in obstruction of the inflow cannula. The cannula was subsequently repositioned. Seven days after VAD implantation, the patient was transferred to the coronary care unit. The remaining post-operative period was uneventful and patient is about to be discharged home.

Peri-operative challenges in the first case included the lack of space between the SRV and the sternum, and the trabeculations in the SRV. The former resulted in mid-basal insertion of the VAD instead of the more apical position that is common for VAD implantation in the left ventricle (*Figs. 1 and 2*). The latter necessitated resection of multiple trabeculations to prevent obstruction of the inflow cannula. The need for resection of trabeculations was expected in both cases, as pre-operative imaging clearly showed a heavily trabeculated SRV in both patients. This approach has been described previously [5]. In our second case, in addition to resection of trabeculations, a different surgical approach was used because of a relatively dorsolateral position of the SRV. In both patients, the challenging positioning of the inflow cannula could be partially explained by the presence of a tricuspid valve prosthesis, making TEE-guided localisation of optimal inflow cannula position less evident.

In general, SRV patients may have complex cardiac and thoracic anatomy, for example dextrocardia or situs inversus. As these cases demonstrate, anatomical variations in SRV patients require a patient-tailored surgical approach for VAD implantation (median (re)sternotomy versus lateral thoracotomy and upper hemisternotomy). An alternative

device position should be considered when lack of space prevents apical implantation of the VAD, and inflow cannula orientation is of paramount importance for unobstructed VAD inflow. Pre-, intra- and post-operative imaging (for example with computed tomography angiography, epicardial/transoesophageal echocardiography, and transthoracic echocardiography, respectively) is crucial to plan and evaluate the operative approach [6].

Patients with SRV failure are potentially good VAD candidates

Donor hearts are scarce in the Netherlands, a problem which is likely to persist. The three cardiac transplantation centres in the Netherlands together currently perform over 30 transplantations per year [7–9] but the demand is much higher. Furthermore, SRV patients are often unsuitable candidates for cardiac transplantation because of 1) unfavourable anatomy; 2) prior surgical procedures and/or 3) physiology [10]. In the usual LVAD population, right ventricular function is an important clinical predictor for morbidity and mortality after LVAD implantation [11, 12]. However, patients with SRV usually have a preserved function of the subpulmonary left ventricle, which is capable of supporting higher pressures without problems, and may be retrained, even in adult patients [13]. Therefore, selected patients with end-stage SRV failure (see *Tab. 1*) may be suitable candidates for VAD implantation as destination therapy. This report demonstrates that this is feasible and leads to significant clinical improvement. Data from the INTERMACS registry concerning all reported VAD implantations in patients with CHD, including patients with SRV, show comparable survival rates between CHD and non-CHD patients at 2 years after implantation [14]. However, VAD implantation is also associated with significant complications and requires dedicated teams to optimise results as demonstrated in the current cases. Still, these complications are similar to the complications reported in the LVAD population with normal anatomy [15, 16].

Table 1: Medical eligibility criteria and contraindications for VAD implantation as destination therapy in patients with SRV, according to our dedicated team

Major criteria for VAD eligibility (all should apply)	VAD contraindicated if one/more of the following
End-stage SRV failure (NYHA IIIb–IV, INTERMACS II–IV)	INTERMACS I
Despite optimal medical therapy	Severe non-cardiac comorbidity with life expectancy <1 year
Despite optimal treatment of tricuspid valve regurgitation	Poor subpulmonary LV function
Despite CRT if indicated	Non-reversible severe kidney dysfunction (eGFR <30 ml/min/1.73m2)
Despite effort to sustain sinus rhythm	Active systemic infection
Ineligible for cardiac transplantation	Unacceptably high operative risk

VAD *ventricular assist device,* SRV *systemic right ventricle,* NYHA *New York Heart Association,* INTERMACS *Interagency Registry for Mechanically Assisted Circulatory Support LV left ventricle,* CRT *cardiac resynchronisation therapy,* eGFR *estimated glomerular filtration rate*

Conclusion

In conclusion, VAD implantation as destination therapy should be considered in patients with severe SRV failure. Despite the risk of complications, VAD therapy is a reasonable option in patients with failing SRV but requires a dedicated and experienced team.

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Chapter 10

Summary, conclusions, and future perspectives

The aims of this thesis were to clarify the physiology and pathophysiology of the systemic right ventricle, with a specific focus on autonomic function (part I: physiology and mechanisms) in relation to clinical outcome, and to explore diagnostic and treatment options (part II: clinical applications). Below, the chapters will be summarized and placed within the context of current literature. Future perspectives will be given per topic.

Part I: (patho)physiology and mechanisms

In the first three chapters, several mechanisms underlying (systemic) ventricular physiology and disease were explored. In **chapter 1**, current knowledge regarding asymmetry and heterogeneity in cardiac autonomic innervation was reviewed. Knowledge about the cardiac autonomic nervous system is necessary to understand and to treat cardiac disease. The heart is an asymmetrical organ, and also cardiac autonomic innervation demonstrates left-right as well as regional differences in anatomy and function. This may have relevant clinical implications. For example, the left and right stellate ganglia and the left and right vagus nerves innervate different areas of the heart or have different effects on the same area (1, 2). In particular, the left stellate ganglion appears to play an important role in ventricular arrhythmias and is an important treatment target, which is not the case for the right stellate ganglion (3, 4).

In **chapter 2 and 3**, three categories of ambulatory ECG-derived measures of cardiac autonomic function were investigated in patients with a systemic right ventricle: *heart rate variability*, *QT-interval variability*, and *heart rate turbulence*. In **chapter 2**, we conclude that in patients with a systemic RV, the heart rate variability component of SDANN (standard deviation of the average normal-to-normal intervals calculated over 5-minute intervals) was independently associated with the occurrence of supraventricular tachycardias. This is clinically relevant as previous studies show that supraventricular arrhythmias are independently associated with sudden cardiac death and mortality in patients with a systemic RV (5-7). Several components of heart rate variability were also correlated with systemic RV function, while in the cohort as a whole, the systemic RV function was relatively preserved. This may indicate the usefulness of heart rate variability to predict clinically overt systemic RV failure. In **chapter 3**, we conclude that components of both QT interval variability and heart rate turbulence were also associated with supraventricular tachycardias. Medication use, including flecainide, diuretics, and ACE inhibitors/ARBs, was also associated with QT variability and heart rate turbulence components, which may indicate that a worse clinical status of these patients is reflected in their autonomic function. Interestingly, heart rate turbulence was worse in patients who underwent recent thoracic surgery but not in patients who underwent one or multiple thoracic surgeries longer ago,

indicating the ability of the cardiac innervation to regenerate after surgical trauma. Future studies might investigate the effects of autonomic modulation, for example vagus nerve stimulation, in patients with a systemic RV. Currently, carefully optimistic results are available for patients with LV disease (8). Heart rate variability, QT interval variability, and heart rate turbulence may be investigated further for their potential to predict clinical deterioration and their possible response to autonomic modulation therapies.

Part II: clinical applications

In **chapter 5**, we concluded that, while echocardiographical assessment of systemic RV function is challenging, several echocardiographic variables are highly feasible and perform well compared with cardiac magnetic resonance, which is considered the gold standard. These variables include *visual estimation of global function*, *fractional area change*, and especially *global longitudinal strain*. Conceptually sound variables such as the *myocardial performance index* may also perform well in patients with LV disease (9) or selected, less complex groups of patients with a systemic RV (10). However, the population we describe reflects the heterogeneous and complex population that is seen in daily clinical practice. The measurement of fractional area change, global longitudinal strain, and the visual estimation of RV function may be implemented in routine echocardiographic protocols for the follow-up of patients with a systemic RV.

In **chapter 6**, the clinical course of patients long after Mustard or Senning correction of TGA was characterized and a risk score to predict major clinical events was distilled from the data. The score requires the often readily available information regarding current age, age at atrial switch operation, prior ventricular arrhythmia, moderate or severe systemic RV dysfunction, severe tricuspid valve regurgitation, and mild or greater subpulmonary LV dysfunction. This risk score may be used in the counseling of patients in the outpatient clinic or in the process of deciding the frequency and intensity of follow-up. Previous studies addressing risk stratification have mainly focused on the group of adults of congenital heart disease as a whole, for example in the need for implantable cardioverter-defibrillator therapy (11), or heart failure (12). However, since the group of adults with congenital heart disease is very heterogeneous, the risk score described in chapter 6 may be more useful in the group of systemic RV patients after Mustard or Senning correction.

Chapter 7 describes the first results of the treatment of systemic right ventricular failure with sacubitril/valsartan. After six months of follow-up, NT-pro-BNP was significantly decreased, echocardiographic systemic RV function showed a small but significant improvement, and 6-minute walking distance and some aspects of quality of

life also showed improvement. Considering that the current ESC guidelines do not recommend specific medical treatment of systemic RV failure yet (13), these results are an important step forward towards expanding and standardizing the medical treatment of systemic RV failure. More evidence is needed to translate these preliminary results into standard clinical practice. In the future, hopefully, the options for medical treatment of systemic RV failure will be expanded with other medications such as SGLT2-inhibitors (14).

Chapter 8 describes the experience of the application of eHealth smart technology in the titration of sacubitril/valsartan in the cohort of **Chapter 7** consisting of patients with systemic RV failure. The patient adherence was high: 83,3% of patients submitted measurements twice a week during the titration process. The satisfaction with the implementation of this technology was 95,5%. For the 24 patients included, 68 trips to the hospital were prevented when compared with the conventional titration process. In one patient (4,2%) a heart failure-related hospital admission was not prevented despite sending in measurements and subsequent contact moments, according to protocol. The possibilities of eHealth are not limited to the measurement of blood pressure, weight, daily steps taken, and the detection of arrhythmias, as described here, but measurement of oxygen saturation and even remote physical activity interventions are being tested in patients with congenital heart disease (15, 16)

In **chapter 9**, we report the first two cases of implantation of a ventricular assist device into a failing systemic RV. At the time of writing, both patients were doing well and had experienced no more complications than can be expected in the usual patient category of LV failure (two early reoperations, one ischemic stroke with mild cognitive sequelae, and a hemodynamically well-tolerated VT, for both patients in total). The implantation of a ventricular assist device may be an attractive option for patients with end stage systemic RV failure. Due to factors such as a complex anatomy or the presence of pulmonary hypertension, they are likely to be rejected for cardiac transplantation, and the function of the subpulmonary LV function is often preserved. In the future, the number of systemic RV patients who might benefit from implantation of a ventricular assist device (either as bridge to transplant or as destination therapy) is expected to increase as the generation of systemic RV patients becomes older and the shortage of donor organs is expected to persist. For patients with concomitant subpulmonary LV dysfunction, a total artificial heart might also become a feasible treatment modality (17).

In conclusion, adult congenital heart disease patients with a systemic RV comprises a complex patient group in whom a myriad of long-term complications can be observed. The work highlighted in this thesis will form the base for ongoing studies aimed at improving outcome and quality of life of this vulnerable group.

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Samenvatting, conclusies, en toekomstperspectieven

De doelstellingen van dit proefschrift waren om de fysiologie en pathofysiologie van de systemische rechterventrikel te verduidelijken, met een specifieke focus op anatomische functie (deel I: fysiologie en mechanismen) in relatie met klinische uitkomsten, en om diagnostische modaliteiten en behandelopties te verkennen (deel II: klinische toepassingen). Hieronder zullen de hoofdstukken worden samengevat en in de context van de huidige literatuur worden geplaatst. Toekomstperspectieven zullen per onderwerp worden vermeld.

Deel I: (patho)fysiology en mechanismen

In de eerste drie hoofdstukken werden meerdere mechanismen onderliggend aan (systemische) rechterventrikelfysiologie en -ziekte verkend. In **hoofdstuk 1** werd de huidige kennis met betrekking tot asymmetrie en heterogeniteit gereviewd. Kennis van het cardiale autonome zenuwstelsel is noodzakelijk om hartziekten te begrijpen en te behandelen. Het hart is een asymmetrisch orgaan, en ook cardiale autonome innervatie heeft links-rechtsverschillen en regionale verschillen in anatomie en functie. Dit kan relevante klinische gevolgen hebben. Bijvoorbeeld, het linker en rechter ganglion stellatum en de linker en rechter nervus vagus innerveren verschillende delen van het hart of hebben verschillende effecten op hetzelfde gebied (1, 2). Specifiek lijkt het linker ganglion stellatum een belangrijke rol te spelen in ventriculaire aritmieën en het is een belangrijk target voor behandeling. Dit is niet het geval bij het rechter ganglion stellatum (3, 4).

In **hoofdstuk 2 en 3** werden drie categorieën van Holter-afgeleide maten van cardiale autonome functie onderzocht in patiënten met een systemische rechterventrikel: *hartslagvariabiliteit, QT-intervalvariabiliteit, en hartslagturbulentie*. In **hoofdstuk 2** concluderen we dat in patiënten met een systemische rechterventrikel, de hartslagvariabiliteitscomponent SDANN (*standard deviation of the average normal-to-normal intervals calculated over 5-minute intervals*) onafhankelijk geassocieerd was met het vóórkomen van supraventriculaire tachycardieën. Dit is klinisch relevant aangezien eerdere studies aantonen dat supraventriculaire tachycardieën onafhankelijk geassocieerd zijn met plotse hartdood en mortaliteit in patiënten met een systemische rechterventrikel (5-7). Meerdere componenten van hartslagvariabiliteit waren ook gecorreleerd met systemische rechterventrikelfunctie, terwijl in het gehele cohort de systemische rechterventrikelfunctie relatief behouden was. Dit zou op het nut van hartslagvariabiliteit kunnen wijzen om klinisch aanwezig systemisch rechterventrikelfalen te voorspellen. In **hoofdstuk 3** concluderen we dat componenten van zowel QT-intervalvariabiliteit als hartslagturbulentie ook geassocieerd waren met supraventriculaire tachycardieën. Medicatiegebruik, inclusief flecainide, diuretica, en ACE-remmers/ARB's, was ook geassocieerd met componenten van QT-

intervalvariabiliteit en hartslagturbulentie, wat erop kan wijzen dat een slechtere klinische status van deze patiënten teruggezien kan worden in hun autonome functie. Interessant genoeg was de hartslagturbulentie slechter in patiënten die recente thoraxchirurgie hadden ondergaan maar niet in patiënten die langer geleden één of meerdere thoraxchirurgische ingrepen hadden ondergaan, wat wijst op het vermogen van cardiale innervatie om te herstellen na chirurgisch trauma. Toekomstige studies zouden de effecten van autonome modulatie, bijvoorbeeld vagusstimulatie, kunnen onderzoeken in patiënten met een systemische rechterventrikel. Op dit moment zijn van dergelijke interventies voorzichtig optimistische resultaten beschikbaar voor patiënten met linkerventrikelaandoeningen (8). Hartslagvariabiliteit, QT-intervalvariabiliteit, en hartslagturbulentie zouden verder onderzocht kunnen worden met betrekking tot het potentieel om clinische achteruitgang te onderzoeken, en de respons van deze maten op autonome modulatietherapie.

Deel II: klinische toepassingen

In **hoofdstuk 5** concluderen we dat, ondanks dat het echocardiografisch beoordelen van de systemische rechterventrikelfunctie uitdagend is, meerdere echocardiografische variabelen goed haalbaar zijn en en goed overeen komen met cardiale magnetische resonantie, wat wordt gezien als de gouden standaard. Deze variabelen zijn *visual estimation of global function, fractional area change*, en met name *global longitudinal strain*. Conceptueel goede variabelen zoals de *myocardial performance index* kunnen goed werken in patiënten met linkerventrikelaandoeningen (9) of geselecteerde, minder complexe groepen van patiënten met een systemische rechterventrikel (10). Echter, de populatie die wij beschrijven, reflecteert de heterogene en complexe populatie die in de dagelijkse praktijk wordt gezien. Het meten van fractional area change, global longitudinal strain, en het verrichten van de visual estimation of global function zou geïmplementeerd kunnen worden in routinematige echocardiografische protocollen voor de follow-up van patiënten met een systemische rechterventrikel.

In **hoofdstuk** 6 werd het klinische beloop gekarakteriseerd van patiënten lange tijd na chirurgische correctie van transpositie van de grote vaten volgens Mustard of Senning, en werd een risicoscore om major clinical events te voorspellen uit de data gedestilleerd. De score vereist meestal direct beschikbare informatie met betrekking tot huidige leeftijd, leeftijd ten tijde van de atriale switchoperatie, eerdere ventriculaire aritmie, matige of ernstige rechterventrikeldysfunctie, ernstige tricuspidalisklepregurgitatie, en ten minste milde subpulmonale linkerventrikeldysfunctie. Deze risicoscore kan gebruikt worden bij het counselen van poliklinische patiënten of bij het beslissen van de frequentie en intensiteit van de follow-up. Eerdere studies over risicostratificatie betroffen met name de groep van

volwassenen met aangeboren hartziekten in zijn geheel, bijvoorbeeld voor *implantable cardioverter-defibrillator*-therapie (11), of hartfalen (12). Echter, aangezien de groep volwassenen met aangeboren hartziekten erg heterogeen is, kan de risicoscore beschreven in hoofdstuk 6 bruikbaarder zijn in de groep van patiënten met een systemische rechterventrikel na correctie volgens Mustard of Senning.

Hoofdstuk 7 beschrijft de eerste resultaten van de behandeling van systemisch rechterventrikelfalen met sacubitril/valsartan. Na zes maanden follow-up was het NT-pro-BNP significant afgenomen, toonde echocardiografische systemische rechterventrikelfunctie een kleine maar significante verbetering, en toonden de 6-*minute walking distance* en sommige aspecten van kwaliteit van leven ook verbetering. Aangezien de huidige ESC-richtlijnen nog geen specifieke medicamenteuze therapie aanraden voor systemisch rechterventrikelfalen (13), zijn deze resultaten een belangrijke stap naar het uitbreiden en standaardiseren van de behandeling van systemisch rechterventrikelfalen. Er zijn nog meer data nodig om deze preliminaire bevindingen te vertalen naar de standaard klinische praktijk. Hopelijk zullen in de toekomst de opties voor de medicamenteuze behandeling van systemisch rechterventrikelfalen worden uitgebreid met andere middelen, bijvoorbeeld SGLT2-remmers (14).

Hoofdstuk 8 beschrijft de ervaring van het toepassen van *eHealth smart technology* in het titreren van sacubitril/valsartan in het cohort van **hoofdstuk 7** bestaande uit patiënten met systemisch rechterventrikelfalen. De therapietrouw was hoog: 83,3 van de patiënten stuurden tweemaal per week metingen in tijdens het titratieproces. De tevredenheid met de implementatie van de technologie van 95,5%. Voor de 24 geïncludeerde patiënten werden 68 bezoeken aan het ziekenhuis voorkomen vergeleken met het conventionele titratieproces. In één patiënt (4,2%) kon een hartfalengerelateerde ziekenhuisopname niet worden voorkomen ondanks het insturen van metingen en daaropvolgende contactmomenten volgens protocol. De mogelijkheden van eHealth zijn niet beperkt tot het meten van bloeddruk, gewicht, dagelijkse stappen, en het detecteren van aritmieën, zoals hier beschreven, maar de meting van zuurstofsaturatie en zelfs lichamelijke activiteitsinterventies worden onderzocht in patiënten met aangeboren hartziekten (15, 16).

In **hoofdstuk 9** beschrijven we de eerste twee gevallen van implantatie van een *ventricular assist device* in een falende systemische rechterventrikel. Ten tijde van het schrijven, ging het met beide patiënten goed en hadden ze niet méér complicaties ondervonden dan te verwachten is in de gebruikelijke patiëntencategorie van linkerventrikelfalen (twee vroege re-operaties, één ischemisch cerebrovasculair event

met milde cognitieve gevolgen, en een hemodynamisch goed verdragen ventriculaire tachycardie, voor beide patiënten gezamenlijk). De implantatie van een *ventricular assist device* kan een aantrekkelijke optie zijn voor patiënten met eindstadium systemisch rechterventrikelfalen. Wegens factoren zoals een complexe anatomie of de aanwezigheid van pulmonale hypertensie worden deze patiënten waarschijnlijk afgewezen voor harttransplantatie, en de functie van de subpulmonale linkerventrikel is vaak behouden. In de toekomst zal het aantal patiënten met een systemische rechterventrikel die baat kunnen hebben bij de implantatie van een *ventricular assist device* (als overbrugging naar transplantatie of als *destination therapy*) waarschijnlijk toenemen gezien de toenemende leeftijd van deze populatie en aangezien het tekort aan donororganen waarschijnlijk zal persisteren. Voor patiënten die tevens subpulmonale linkerventrikeldysfunctie hebben, zou een *total artificial heart* een haalbare behandelmodaliteit kunnen worden (17).

In conclusie, volwassen patiënten met een aangeboren hartziekte met een systemische rechterventrikel zijn een complexe patiëntengroep waarin een veelheid aan langetermijncomplicaties wordt gezien. De studies in dit proefschrift vormen een basis voor toekomstige studies gericht op het verbeteren van klinische uitkomsten en kwaliteit van leven in deze kwetsbare groep.

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Curriculum Vitae

Tjitske Elisabeth Zandstra werd op 12 mei 1992 geboren in Drachten. In 2010 haalde zij cum laude haar Gymnasiumdiploma aan het Drachtster Lyceum in Drachten. In 2016 behaalde zij haar geneeskundediploma aan de Rijksuniversiteit Groningen. Tijdens de bachelor heeft zij het bachelor Honours College traject met succes afgerond en heeft zij frequent deelgenomen aan debattoernooien en ook met regelmaat debattrainingen gegeven aan diverse partijen. Haar seniorcoschappen heeft ze gelopen in het Röpcke-Zweersziekenhuis in Hardenberg. Haar stage wetenschap in het UMCG, onder begeleiding van dr. P.G. Pieper, betrof inspanningsvermogen en kwaliteit van leven bij volwassen patiënten met een aangeboren hartafwijking en een hartklepprothese. Nadat ze een half jaar als ANIOS (arts niet in opleiding tot specialist) had gewerkt bij de cardiologie in het LUMC, is zij daar in 2017 gestart met een promotietraject binnen de congenitale cardiologie, onder prof. dr. M.J. Schalij als promotor en dr. M.R.M. Jongbloed (inmiddels prof. dr. Jongbloed en promotor) en dr. P. Kiès als copromotoren. Tijdens dit traject was zij tevens LVAD-coördinator (left ventricular assist device), een taak met verantwoordelijkheden in patiëntenzorg en onderwijs rondom LVAD-patiënten, onder begeleiding van dr. S.L.M.A. Beeres en dr. L.F. Tops. In 2020 is zij als ANIOS gaan werken bij de cardiologie in het MST te Enschede, waar zij in 2021 begonnen is met de vooropleiding interne geneeskunde in het kader van de opleiding tot cardioloog onder opleider dr. P.J. Verhorst. Zij is overgestapt naar de opleiding tot internist in het MST onder opleider dr. M.C. Legdeur (en vanuit het UMCG onder opleider prof. dr. T.P. Links) en heden bezig met het tweede opleidingsjaar.